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APPLICATION NUMBER: *60/438,540*
FILING DATE: *January 06, 2003*
RELATED PCT APPLICATION NUMBER: *PCT/US03/39120*

RECEIVED
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01/09/03 30438540 .01 Approved

Modified PTO/SB/16 (6-95)
Approved for use through 04/11/98. OMB 0651-0037
Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

01/06/03 JC892 U.S. PTO

PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53 (c)

Docket Number	P-15460	Type a plus sign (+) inside this box –>	+

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JC400 U.S. PTO 60/438540 01/06/03

TITLE OF THE INVENTION (280 characters max)

FUSED HETEROCYCLIC DERIVATIVES AS PPAR MODULATORS

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STATE	IN	ZIP CODE	46206-6288	COUNTRY	USA

ENCLOSED APPLICATION PARTS (*check all that apply*)

X	Specification	Number of pages	100		Small Entity Statement	
	Drawing(s)	Number of Sheets			Other (Specify)	

METHOD OF PAYMENT (*check one*)

			PROVISIONAL FILING FEE AMOUNT ($)	$160.00
	A check or money order is enclosed to cover the Provisional filing fees			
X	The Assistant Commissioner is hereby authorized to charge filing fees and credit Deposit Account Number:	05-0840		

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

[X] No.

[ ] Yes, the name of the U.S. Government agency and the Government contract number are:

Respectfully submitted,
SIGNATURE MaCharri Vorndran-Jones Date 1 / 6 / 03

TYPED or PRINTED NAME MACHARRI VORNDRAN-JONES

REGISTRATION NO. (*if appropriate*) 36,711

[ ] Additional inventors are being named on separately numbered sheets attached hereto

PROVISIONAL APPLICATION FOR PATENT FILING ONLY

"Express Mail" mailing label number EL342552189US Date of Deposit 1-6-03
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Jennifer L. Barker
Signature

FUSED HETEROCYCLIC DERIVATIVES AS PPAR MODULATORS

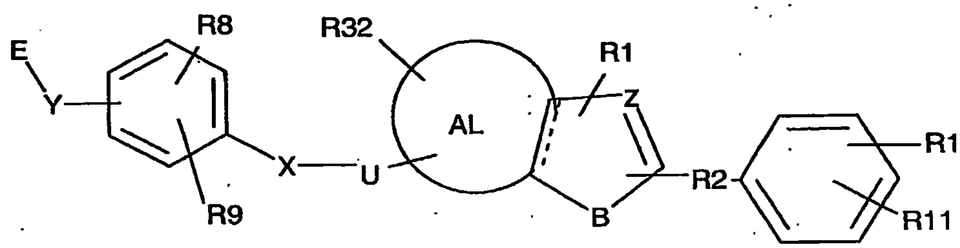
BACKGROUND OF THE INVENTION

Peroxisome Proliferator Activated Receptors (PPARs) are members of the nuclear hormone receptor super family, which are ligand-activated transcription factors regulating gene expression. Various subtypes of PPARs have been discovered. These include, for example, PPARα, NUC1, PPARγ and PPARδ. PPARα, PPARγ and PPARδ receptors have been implicated in diabetes mellitus, cardiovascular disease, obesity, Syndrome X and gastrointestinal disease, such as, inflammatory bowel disease. Syndrome X is the combination of symptoms which include hyperinsulemia combined with hypertension, elevated body weight, elevated triglycerides and elevated LDL. Current PPAR agonist treatment for Syndrome X relates to the use of thiazolidinediones (TZDs) or other insulin sensitivity enhancers (ISEs). A need exists for new pharmaceutical agents which affect treat or prevent cardiovascular disease, particularly that associated with Syndrome X, while preventing or minimizing weight gain, and

more preferably while improving insulin sensitivity. It may be especially desirable when the active pharmaceutical agent selectively modulates a PPAR receptor subtype to provide an especially desirable pharmacological profile. In some instances, it can be desirable when the active pharmacological agent selectively modulates more than one PPAR receptor subtype to provide a desired pharmacological profile.

SUMMARY OF THE INVENTION

The present invention is directed to compounds represented by the following structural Formula I:



and stereoisomers, pharmaceutically acceptable salts, solvates and hydrates thereof, wherein:

(a) R1 is selected from the group consisting of hydrogen, C_1-C_8 alkyl, C_1-C_8 alkenyl, aryl-C_{0-4}-alkyl, aryl-C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, C3-C6 cycloalkylaryl-C_{0-2}-alkyl, and, wherein C_1-C_8 alkyl, C_1-C_8 alkenyl, aryl-C_{0-4}-alkyl, aryl-C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, C3-C6 cycloalkylaryl-C_{0-2}-alkyl are each optionally substituted with from one to three substituents independently selected from R1';

(b) R1', R26, R27, R28 and R31 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkyl-COOR12, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkyloxy, C_3-C_7 cycloalkyl, aryloxy, aryl-C_{0-4}-alkyl, heteroaryl, heterocycloalkyl, C(O)R13, COOR14, OC(O)R15, $OS(O)_2R16$, $N(R17)_2$, NR18C(O)R19, $NR20SO_2R21$, SR22, S(O)R23, $S(O)_2R24$, and $S(O)_2N(R25)_2$; R12, R13, R14, R15, R16, R17, R18, R19, R20, R21, R22, R23, R24 and R25 are each independently selected from the group consisting of hydrogen, C_1-C_6 alkyl and aryl;

(c) R2 is selected from the group consisting of C_0-C_8 alkyl and C_{1-4}-heteroalkyl;

(d) X is selected from the group consisting of a single bond, O, S, $S(O)_2$ and N;

(e) U is an aliphatic linker wherein one carbon atom of the aliphatic linker may be replaced with O, NH or S, and wherein such aliphatic linker is optionally substituted with R30;

(f) Y is selected from the group consisting of C, O, S, NH and a single bond;

(g) E is C(R3)(R4)A or A and wherein

(i) A is selected from the group consisting of carboxyl, tetrazole, C_1-C_6 alkylnitrile, carboxamide, sulfonamide and acylsulfonamide; wherein sulfonamide, acylsulfonamide and tetrazole are each optionally substituted with from one to two groups independently selected from R^7;

(ii) each R^7 is independently selected from the group consisting of hydrogen, C_1-C_6 haloalkyl, aryl C_0-C_4 alkyl and C_1-C_6 alkyl;

(iii) R3 is selected from the group consisting of hydrogen, C_1-C_5 alkyl, and C_1-C_5 alkoxy; and

(iv) R4 is selected from the group consisting of H, C_1-C_5 alkyl, C_1-C_5 alkoxy, aryloxy, C_3-C_6 cycloalkyl, and aryl C_0-C_4 alkyl, and R3 and R4 are optionally combined to form a C_3-C_4 cycloalkyl, and wherein alkyl, alkoxy, aryloxy, cycloalkyl and aryl-alkyl are each optionally substituted with one to three substituents each independently selected from R26;

(h) B is selected from the group consisting of S, O, C, and N, with the proviso that when B is N then Z is C;

(i) Z is selected from the group consisting of N and C, with the proviso that when B is C then Z is N;

(j) R8 is selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_1-C_4 alkylenyl, and halo;

(k) R9 is selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_1-C_4 alkylenyl, halo, aryl-C_0-C_4 alkyl, heteroaryl, C_1-C_6 allyl, and OR29, and wherein aryl-C_0-C_4 alkyl, heteroaryl are each optionally substituted with from one to three independently selected from R27; R29 is selected from the group consisting of hydrogen and C_1-C_4 alkyl;

(l) R10, R11 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkyl-COOR12'', C_0-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6

haloalkyloxy, C_3-C_7 cycloalkyl, aryl-C_{0-4}-alkyl, aryl- C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, C3-C6 cycloalkylaryl-C_{0-2}-alkyl, aryloxy, C(O)R13′, COOR14′, OC(O)R15′, $OS(O)_2R16'$, $N(R17')_2$, NR18′C(O)R19′, $NR20'SO_2R21'$, SR22′, S(O)R23′, $S(O)_2R24'$, and $S(O)_2N(R25')_2$; and wherein aryl-C_{0-4}-alkyl, aryl- C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl are each optionally substituted with from one to three substituents independently selected from R28;

(m) R12′, R12′′, R13′, R14′, R15′, R16′, R17′, R18′, R19′, R20′, R21′, R22′, R23′, R24′, and R25′ are each independently selected from the group consisting of hydrogen, C_1-C_6 alkyl and aryl;

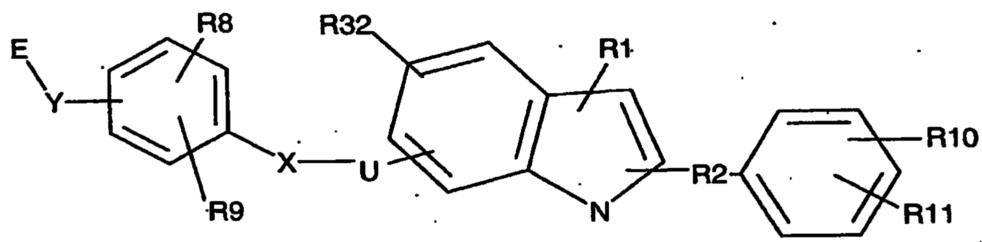
(n) R30 is selected from the group consisting of C_1-C_6 alkyl, aryl-C_{0-4}-alkyl, aryl- C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl, and wherein C_1-C_6 alkyl, aryl-C_{0-4}-alkyl, aryl- C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl are each optionally substituted with from one to three substituents each independently selected from R31;

(o) R32 is selected from the group consisting of a bond, hydrogen, halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, and C_1-C_6 alkyloxo;

(p) AL is selected from the group consisting of a fused C_3-C_8 carbocyclic and a fused phenyl; and

(q) ---- is optionally a bond to form a double bond at the indicated position.

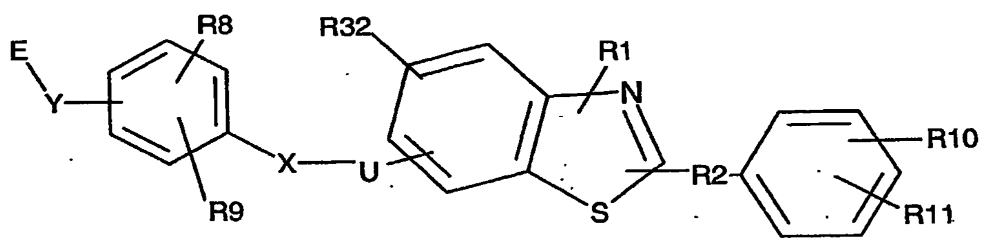
It can be preferred that the compound of this invention is of the structural Formula II:



;

wherein the E, Y, R8, R9, X, U, R1, R32, R2, R10, and R11 are as defined herein above.

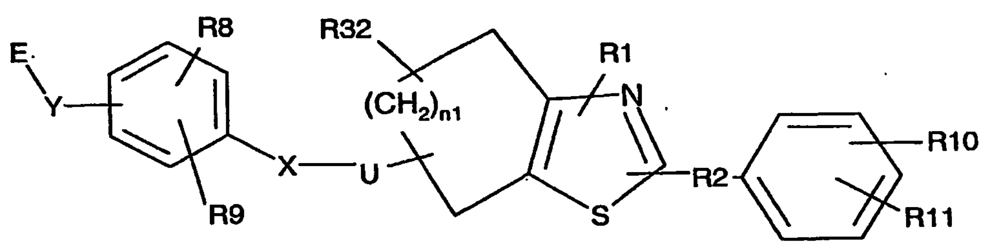
It can be preferred that the compound of this invention is of the structural Formula III:



;

wherein the E, Y, R8, R9, X, U, R1, R32, R2, R10, and R11 are as defined above.

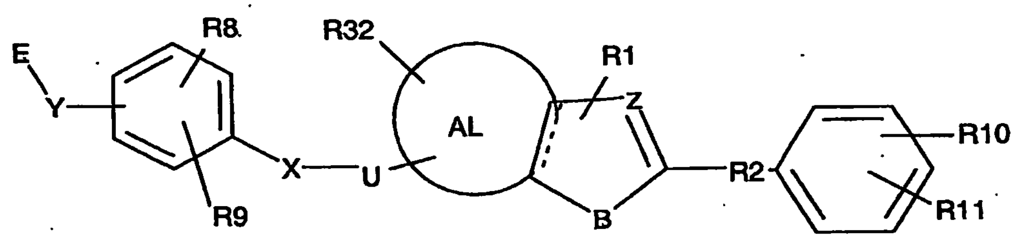
It can be preferred that the compound of this invention is of the Structural Formula IV:



;

wherein E, Y, R8, R9, X, U, R1, R32, R2, R10, and R11 are as defined herein above; n1 is 1 to 5. It is preferred that n1 is 1 to 2.

It can be preferred that the compound of this invention is of the Structural Formula V:



In one embodiment, the present invention also relates to pharmaceutical compositions comprising at least one compound of the present invention, or a pharmaceutically acceptable salt, solvate, hydrate, or stereioisomer thereof, and a pharmaceutically acceptable carrier.

In another embodiment, the present invention relates to a method of selectively modulating a PPAR delta receptor by contacting the receptor with at least one compound represented by Structural Formula I, or a pharmaceutically acceptable salt, solvate, hydrate, or stereioisomer thereof.

In another embodiment, the present invention relates to a method of modulating one or more of the PPAR alpha, beta, gamma, and/or delta receptors.

In a further embodiment, the present invention relates to a method of making a compound represented by Structural Formula I.

The compounds of the present invention are believed to be effective in treating and preventing Syndrome X, Type II diabetes, hyperglycemia, hyperlipidemia, obesity, coagaulopathy, hypertension, atherosclerosis, and other disorders related to Syndrome X and cardiovascular diseases. Further, compounds of this invention can be useful for lowering fibrinogen, increasing HDL levels, treating renal disease, controlling desirable weight, treating demyelinating diseases, treating certain viral infections, and treating liver disease. In addition, the compounds can

be associated with fewer clinical side effects than compounds currently used to treat such conditions.

DETAILED DESCRIPTION OF THE INVENTION

The terms used to describe the instant invention have the following meanings.

As used herein, the term "aliphatic linker" or "aliphatic group" is a non-aromatic, consisting solely of carbon and hydrogen and may optionally contain one or more units of saturation, e.g., double and/or triple bonds (also refer herein as "alkenyl" and "alkynyl"). An aliphatic or aliphatic group may be straight chained, branched (also refer herein as "alkyl") or cyclic (also refer herein as "cycloalkyl). When straight chained or branched, an aliphatic group typically contains between about 1 and about 10 carbon atoms, more typically between about 1 and about 6 carbon atoms. When cyclic, an aliphatic typically contains between about 3 and about 10 carbon atoms, more typically between about 3 and about 7 carbon atoms. Aliphatics are preferably C_1-C_{10} straight chained or branched alkyl groups (i.e. completely saturated aliphatic groups), more preferably C_1-C_6 straight chained or branched alkyl groups. Examples include, but are not limited to methyl, ethyl, propyl, n-propyl, iso-propyl, n-butyl, sec-butyl, and tert-butyl. Additional examples include, but are not limited to,

cyclopropyl, cyclopentyl, cyclohexyl, cyclopentyl, cyclohexylyl and the like.

The term "alkyl," unless otherwise indicated, refers to those alkyl groups of a designated number of carbon atoms of either a straight or branched saturated configuration. As used herein, "C_0 alkyl" means that there is no carbon and therefore represents a bond. Examples of "alkyl" include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl, pentyl, hexyl, isopentyl and the like. Alkyl as defined above may be optionally substituted with a designated number of substituents as set forth in the embodiment recited above. As used herein, the term "alkyloxo" means an alkyl group of the designated number of carbon atoms with a "=O" substituent.

The term "alkenyl" means hydrocarbon chain of a specified number of carbon atoms of either a straight or branched configuration and having at least one carbon-carbon double bond, which may occur at any point along the chain, such as ethenyl, propenyl, butenyl, pentenyl, vinyl, alkyl, 2-butenyl and the like. Alkenyl as defined above may be optionally substituted with designated number of substituents as set forth in the embodiment recited above.

The term "alkynyl" means hydrocarbon chain of a specified number of carbon atoms of either a straight or branched configuration and having at least one carbon-carbon triple bond, which may occur at any point along the chain. Example of alkynyl is acetylene. Alkynyl as defined above may be optionally substituted with designated number of substituents as set forth in the embodiment recited above.

The term "heteroalkyl" refers to a means hydrocarbon chain of a specified number of carbon atoms

wherein at least one carbon is replaced by a heteroatom selected from the group consisting of O, N and S.

The term "cycloalkyl" refers to a saturated or partially saturated carbocycle containing one or more rings of from 3 to 12 carbon atoms, typically 3 to 7 carbon atoms. Examples of cycloalkyl includes, but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, and the like. "Cycloalkyaryl" means that an aryl is fused with a cycloalkyl, and "Cycloalkylaryl-alkyl" means that the cycloalkylaryl is linked to the parent molecule through the alkyl. Cycloalkyl as defined above may be optionally substituted with a designated number of substituents as set forth in the embodiment recited above.

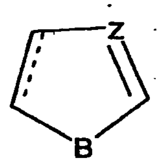
The term "halo" refers to fluoro, chloro, bromo and iodo.

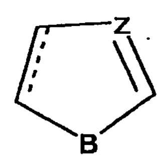
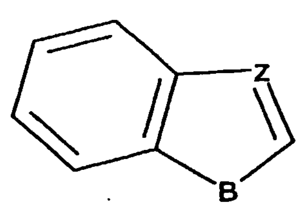
The term "haloalkyl" is a C_1-C_6 alkyl group, which is substituted with one or more halo atoms selected from F, Br, Cl and I. An example of a haloalkyl group is trifluoromethyl (CF_3).

The term "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge, such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, pentoxy, and the like. Alkoxy as defined above may be optionally substituted with a designated number of substituents as set forth in the embodiment recited above.

The term "haloalkyloxy" represents a C_1-C_6 haloalkyl group attached through an oxygen bridge, such as OCF_3. The "haloalkyloxy" as defined above may be optionally substituted with a designated number of substituents as set forth in the embodiment recited above.

The term "aryl" includes carbocyclic aromatic ring systems (e.g. phenyl), fused polycyclic aromatic ring systems (e.g. naphthyl and anthracenyl) and aromatic ring systems fused to carbocyclic non-aromatic ring systems (e.g., 1,2,3,4-tetrahydronaphthyl). "Aryl" as defined above may be optionally substituted with a designated number of substituents as set forth in the embodiment recited above.

As used herein, the term "fused carbocyclic" means an optionally saturated C_3–C_9 ring system that is fused with the  group to form a 7 to 12 member bicyclic ring system. The fused ring system can optionally contain one or more double bonds. Such fused ring system is substituted with R1 and R32, as defined herein.

As used herein, the term "fused phenyl" means that the phenyl ring is fused with the  group to form a bicyclic group of the formula  and wherein such group is substituted with R32 and R1, as defined herein.

The term "arylalkyl" refers to an aryl alkyl group which is linked to the parent molecule through the alkyl group, which may be further optionally substituted with a designated number of substituents as set forth in the embodiment recited above. When arylalkyl is arylC_0alkyl,

then the aryl group is bonded directly to the parent molecule. Likewise, arylheteroalkyl means an aryl group linked to the parent molecule through the heteroalkyl group.

The term "acyl" refers to alkylcarbonyl species.

The term "heteroaryl" group, as used herein, is an aromatic ring system having at least one heteroatom such as nitrogen, sulfur or oxygen and includes monocyclic, bicyclic or tricyclic aromatic ring of 5- to 14-carbon atoms containing one or more heteroatoms selected from the group consisting of O, N, and S. The "heteroaryl" as defined above may be optionally substituted with a designated number of substituents as set forth in the embodiment recited above. Examples of heteroaryl are, but are not limited to, furanyl, indolyl, thienyl (also referred to herein as "thiophenyl") thiazolyl, imidazolyl, isoxazoyl, oxazoyl, pyrazoyl, pyrrolyl, pyrazinyl, pyridyl, pyrimidyl, pyrimidinyl and purinyl, cinnolinyl, benzofuranyl, benzothienyl, benzotriazolyl, benzoxazolyl, quinoline, isoxazolyl, isoquinoline and the like. The term "heteroarylalkyl" means that the heteroaryl group is linked to the parent molecule through the alkyl portion of the heteroarylalkyl.

The term "heterocycloalkyl" refers to a non-aromatic ring which contains one or more oxygen, nitrogen or sulfur and includes a monocyclic, bicyclic or tricyclic non-aromatic ring of 5 to 14 carbon atoms containing one or more heteroatoms selected from O, N or S. The "heterocycloalkyl" as defined above may be optionally substituted with a designated number of substituents as set forth in the embodiment recited above. Examples of heterocycloalkyl include, but are not limited to, morpholine, piperidine, piperazine, pyrrolidine, and thiomorpholine. As used

herein, alkyl groups include straight chained and branched hydrocarbons, which are completely saturated.

As used herein, the phrase "selectively modulate" means a compound whose EC50 for the stated PPAR receptor is at least ten fold lower than its EC50 for the other PPAR receptor subtypes.

When a compound represented by Structural Formula I has more than one chiral substituent it may exist in diastereoisomeric forms. The diastereoisomeric pairs may be separated by methods known to those skilled in the art, for example chromatography or crystallization and the individual enantiomers within each pair may be separated using methods familiar to the skilled artisan. The present invention includes each diastereoisomer of compounds of Structural Formula I and mixtures thereof.

Certain compounds of Structural Formula I may exist in different stable conformational forms which may be separable. Torsional asymmetry due to restricted rotation about an asymmetric single bond, for example because of steric hindrance or ring strain, may permit separation of different conformers. The present invention includes each conformational isomer of compounds of Structural Formula I and mixtures thereof.

Certain compounds of Structural Formula I may exist in zwitterionic form and the present invention includes each zwitterionic form of compounds of Structural Formula I and mixtures thereof.

"Pharmaceutically-acceptable salt" refers to salts of the compounds of the Structural Formula I which are considered to be acceptable for clinical and/or veterinary use. Typical pharmaceutically-acceptable salts include those salts prepared by reaction of the compounds of the

present invention with a mineral or organic acid or an organic or inorganic base. Such salts are known as acid additiona salts and base addition salts, respectively. It will be recognized that the particular counterion forming a part of any salt of this invention is not of a critical nature, so long as the salt as a whole is pharmaceutically-acceptable and as long as the counterion does not contribute undesired qualities to the salt as a whole. These salts may be prepared by methods known to the skilled artisan.

The term, "active ingredient" means the compounds generically described by Structural Formula I as well as the sterioisomers, salts, solvates, and hydrates,

The term "pharmaceutically acceptable" means that the carrier, diluent, excipients and salt are pharmaceutically compatible with the other ingredients of the composition. Pharmaceutical compositions of the present invention are prepared by procedures known in the art using well known and readily available ingredients.

"Preventing" refers to reducing the likelihood that the recipient will incur or develop any of the pathological conditions described herein. The term "preventing" is particularly applicable to a patient that is susceptible to the particular patholical condition.

"Treating" refers to mediating a disease or condition and preventing, or mitigating, its further progression or ameliorate the symptoms associated with the disease or condition.

"Pharmaceutically-effective amount" means that amount of active ingredientit, that will elicit the biological or medical response of a tissue, system, or mammal. Such an amount can be administered prophylactically to a patient thought to be susceptible to development of a disease or

condition. Such amount when administered prophylactically to a patient can also be effective to prevent or lessen the severity of the mediated condition. Such an amount is intended to include an amount which is sufficient to modulate a selected PPAR receptor or to prevent or mediate a disease or condition. Generally, the effective amount of a Compound of Formula I will be between 0.02 through 5000 mg per day. Preferably the effective amount is between 1 through 1,500 mg per day. Preferably the dosage is from 1 through 1,000 mg per day.

The desired dose may be presented in a single dose or as divisded doses administered at appropriate intervals.

A "mammal" is an individual animal that is a member of the taxonomic class Mammalia. The class Mammalia includes humans, monkeys, chimpanzees, gorillas, cattle, swine, horses, sheep, dogs, cats, mice, and rats.

Administration to a human is most preferred. The compounds and compositions of the present invention are useful for the treatment and/or prophylaxis of cardiovascular disease, for raising serum HDL cholesterol levels, for lowering serum triglyceride levels and for lower serum LDL cholesterol levels. Elevated triglyceride and LDL levels, and low HDL levels, are risk factors for the development of heart disease, stroke, and circulatory system disorders and diseases.

The compounds and compositions of the present invention are also useful for treating and/or preventing obesity.

Further, these compounds and compositions are useful for the treatment and/or prophylaxis of non-insulin dependent diabetes mellitus (NIDDM) with reduced or no body weight gains by the patients. Furthermore, the compounds and compositions of the present invention are useful to treat or

prevent acute or transient disorders in insulin sensitivity, such as sometimes occur following surgery, trauma, myocardial infarction, and the like. The physician of ordinary skill will know how to identify humans who will benefit from administration of the compounds and compositions of the present invention.

The present invention further provides a method for the treatment and/or prophylaxis of hyperglycemia in a human or non-human mammal which comprises administering an effective amount of active ingredient, as defined herein, to a hyperglycemic human or non-human mammal in need thereof.

The invention also relates to the use of a compound of Formula I as described above, for the manufacture of a medicament for treating a PPAR receptor mediated condition.

A therapeutically effective amount of a compound of Structural Formula I can be used for the preparation of a medicament useful for treating Syndrome X, diabetes, treating obesity, lowering tryglyceride levels, lowering serum LDL levels, raising the plasma level of high density lipoprotein, and for treating, preventing or reducing the risk of developing atherosclerosis, and for preventing or reducing the risk of having a first or subsequent atherosclerotic disease event in mammals, particularly in humans. In general, a therapeutically effective amount of a compound of the present invention typically reduces serum triglyceride levels of a patient by about 20% or more, and increases serum HDL levels in a patient. Preferably, HDL levels will be increased by about 30% or more. In adition, a therapeutically effective amount of a compound, used to prevent or treat NIDDM, typically reduces serum glucose levels, or more specifically HbA1c, of a patient by about 0.7% or more.

When used herein Syndrome X includes pre-diabetic insulin resistance syndrome and the resulting complications thereof, insulin resistance, non-insulin dependent diabetes, dyslipidemia, hyperglycemia obesity, coagulopathy, hypertension and other complications associated with diabetes. The methods and treatments mentioned herein include the above and encompass the treatment and/or prophylaxis of any one of or any combination of the following: pre-diabetic insulin resistance syndrome, the resulting complications thereof, insulin resistance, Type II or non-insulin dependent diabetes, dyslipidemia, hyperglycemia, obesity and the complications associated with diabetes including cardiovascular disease, especially atherosclerosis.

The compositions are formulated and administered in the same general manner as detailed herein. The compounds of the instant invention may be used effectively alone or in combination with one or more additional active agents depending on the desired target therapy. Combination therapy includes administration of a single pharmaceutical dosage composition which contains a compound of Structural Formula I, a stereoisomer, salt, solvate and/or hydrate thereof ("Active Igredient") and one or more additional active agents, as well as administration of a compound of Active Ingredient and each active agent in its own separate pharmaceutical dosage formulation. For example, an Active Ingredient and an insulin secretogogue such as biguanides, thiazolidinediones, sulfonylureas, insulin, or α-glucosidose inhibitors can be administered to the patient together in a single oral dosage composition such as a tablet or capsule, or each agent administered in separate oral dosage formulations. Where separate dosage formulations are used,

an Active Ingredient and one or more additional active agents can be administered at essentially the same time, i.e., concurrently, or at separately staggered times, i.e., sequentially; combination therapy is understood to include all these regimens.

An example of combination treatment or prevention of atherosclerosis may be wherein an Active Ingredient is administered in combination with one or more of the following active agents: antihyperlipidemic agents; plasma HDL-raising agents; antihypercholesterolemic agents, fibrates, vitamins, aspirin, and the like. As noted above, the Active Ingredient can be administered in combination with more than one additional active agent.

Another example of combination therapy can be seen in treating diabetes and related disorders wherein the Active Ingredient can be effectively used in combination with, for example, sulfonylureas, biguanides, thiazolidinediones, α-glucosidase inhibitors, other insulin secretogogues, insulin as well as the active agents discussed above for treating atherosclerosis.

The Active Ingredients of the present invention, have valuable pharmacological properties and can be used in pharmaceutical compositions containing a therapeutically effective amount of Active Ingredient of the present invention, in combination with one or more pharmaceutically acceptable excipients. Excipients are inert substances such as, without limitation carriers, diluents, fillers, flavoring agents, sweeteners, lubricants, solubilizers, suspending agents, wetting agents, binders, disintegrating agents, encapsulating material and other conventional adjuvants. Proper formulation is dependent upon the route of administration chosen. Pharmaceutical compositions

typically contain from about 1 to about 99 weight percent of the Active Ingredient of the present invention.

Preferably, the pharmaceutical formulation is in unit dosage form. A "unit dosage form" is a physically discrete unit containing a unit dose, suitable for administration in human subjects or other mammals. For example, a unit dosage form can be a capsule or tablet, or a number of capsules or tablets. A "unit dose" is a predetermined quantity of the Active Ingredient of the present invention, calculated to produce the desired therapeutic effect, in association with one or more pharmaceutically-acceptable excipients. The quantity of active ingredient in a unit dose may be varied or adjusted from about 0.1 to about 1500 milligrams or more according to the particular treatment involved. It may be preferred that the unit dosage is from about 1 mg to about 1000 mg.

The dosage regimen utilizing the compounds of the present invention is selected by one of ordinary skill in the medical or veterinary arts, in view of a variety of factors, including, without limitation, the species, age, weight, sex, and medical condition of the recipient, the severity of the condition to be treated, the route of administration, the level of metabolic and excretory function of the recipient, the dosage form employed, the particular compound and salt thereof employed, and the like.

Advantageously, compositions containing the compound of Structural Formula I or the salts thereof may be provided in dosage unit form, preferably each dosage unit containing from about 1 to about 500 mg be administered although it will, of course, readily be understood that the amount of the compound or compounds of Structural Formula I actually

to be administered will be determined by a physician, in the light of all the relevant circumstances.

Preferably, the compounds of the present invention are administered in a single daily dose, or the total daily dose may be administered in divided doses, two, three, or more times per day. Where delivery is via transdermal forms, of course, administration is continuous.

Suitable routes of administration of pharmaceutical compositions of the present invention include, for example, oral, eyedrop, rectal, transmucosal, topical, or intestinal administration; parenteral delivery (bolus or infusion), including intramuscular, subcutaneous, intramedullary injections, as well as intrathecal, direct intraventricular, intravenous, intraperitoneal, intranasal, or intraocular injections. The compounds of the invention can also be administered in a targeted drug delivery system, such as, for example, in a liposome coated with endothelial cell-specific antibody.

Solid form formulations include powders, tablets and capsules.

Sterile liquid formulations include suspensions, emulsions, syrups, and elixirs.

Pharmaceutical compositions of the present invention can be manufactured in a manner that is itself known, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, lyophilizing processes, and/or coupled with soluble polymers as targeted drug carriers.

The following pharmaceutical formulations 1 and 2 are illustrative only and are not intended to limit the scope of the invention in any way.

Formulation 1

Hard gelatin capsules are prepared using the following ingredients:

	Quantity (mg/capsule)
Active Ingredient	250
Starch, dried	200
Magnesium stearate	10
Total	460 mg

Formulation 2

A tablet is prepared using the ingredients below:

	Quantity (mg/tablet)
Active Ingredient	250
Cellulose, microcrystalline	400
Silicon dioxide, fumed	10
Stearic acid	5
Total	665 mg

The components are blended and compressed to form tablets each weighing 665 mg .

In yet another embodiment of the compounds of the present invention, the compound is radiolabelled, such as with carbon-14, or tritiated. Said radiolabelled or tritiated compounds are useful as reference standards for in vitro assays to identify new selective PPAR receptor agonists.

The compounds of the present invention can be useful for modulating insulin secretion and as research

tools. Certain compounds and conditions within the scope of this invention are preferred. The following conditions, invention embodiments, and compound characteristics listed in tabular form may be independently combined to produce a variety of preferred compounds and process conditions. The following list of embodiments of this invention is not intended to limit the scope of this invention in any way.

Some prefered characteristics of compounds of formula I are:

(a) R3 is methyl;
(b) R4 is hydrogen;
(c) R3 is C_1-C_2 alkyl;
(d) R4 is C_1-C_2 alkyl;
(e) R3 and R4 are each hydrogen;
(f) R3 and R4 are each methyl;
(g) A is carboxyl;
(h) X is -O-;
(i) X is -S-;
(j) X is a bond;
(k) U is CH;
(l) U is CH_2CH;
(m) R9 is methyl;
(n) R9 is hydrogen;
(o) R9 is C_1-C_3 alkyl;
(p) R8 is methyl;
(q) R8 and R9 are each hydrogen;
(r) R10 is CF_3;
(s) R10 is haloalkyl;
(t) R10 is haloalkyloxy;
(u) R11 is hydrogen
(v) R10 and R11 are each hydrogen;
(w) R11 is haloalkyl;

(x) Z is N;

(y) Z is C and B is N;

(z) B is S;

(aa) B is O;

(bb) AL is unsaturated;

(cc) AL is saturated;

(dd) AL is aromatic;

(ee) AL is a fused phenyl;

(ff) AL is a fused C_5-C_7 cycloalkyl;

(gg) ---- in the five membered ring each form a double bond at the designated position in Formula I;

(hh) R1 is C_1-C_4 alkyl;

(ii) R32 is hydrogen;

(jj) R2 is a bond;

(kk) R2 is C_1-C_2 alkyl;

(ll) Y is O;

(mm) Y is S;

(nn) Y is C;

(oo) E is C(R3)(R4)A;

(pp) A is COOH;

(qq) Aliphatic linker is saturated;

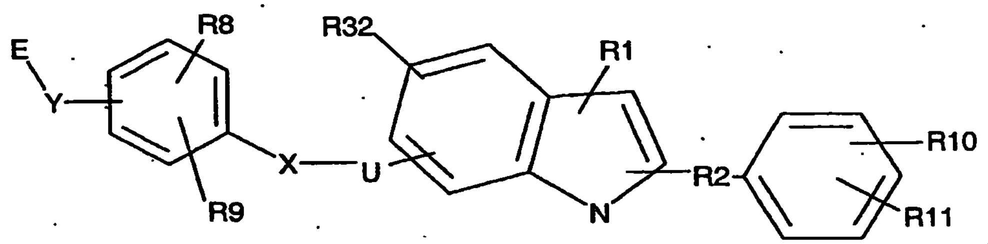
(rr) Aliphatic linker is substituted with C_1-C_3 alkyl;

(ss) Aliphatic linker is C_1-C_3 alkyl;

(tt) Aliphatic linker is C_1-C_2 alkyl;

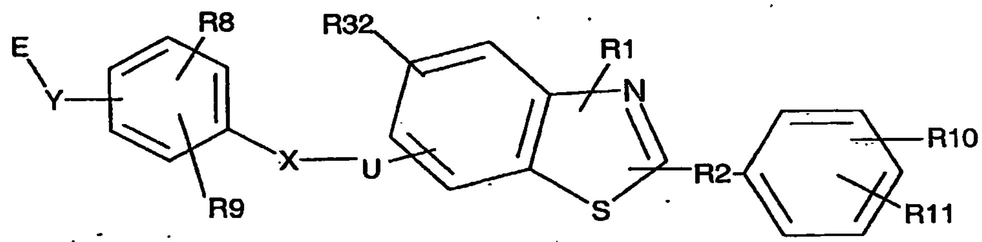
(uu) Aliphatic linker is C_1-C_3 alkyl and one carbon is replaced with an -O-;

(vv) A compound of this invention of the Structural Formula II:



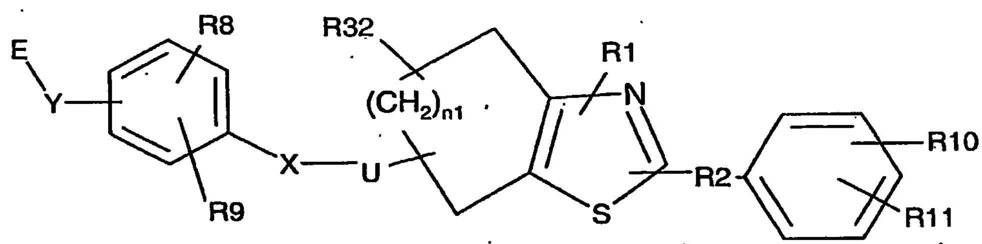
;

(ww) A compound of this invention of the Structural Formula III:



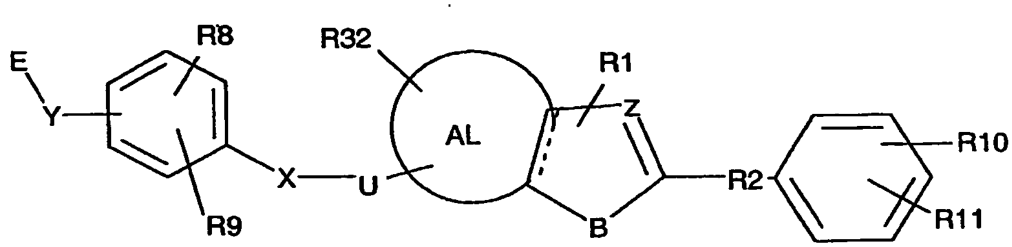
;

(xx) A compound of this invention of the Structural Formula IV:



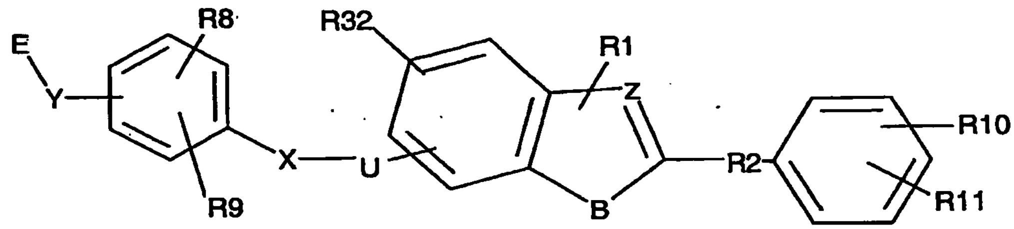
;

(yy) A compound of this invention of the Structural Formula V:



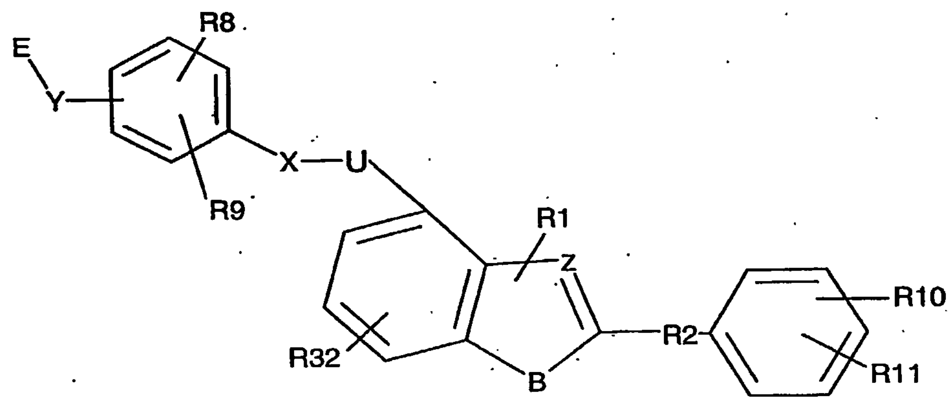
;

(zz) A compound of this invention of the Structural Formula VI:



;

(aaa) A compound of this invention of the Structural Formula VII:



;

(bbb) Aryl is a phenyl group;

(ccc) A compound of Formula I that selectively modulates a delta receptor;

(ddd) An Active Ingredient, as described herein, that is a PPAR coagaonist that modulates a gamma receptor and a delta receptor;

(eee) An Active Ingredient, as described herein, for use in the treatment of cardiovascular disease;

(fff) An Active Ingredient, as described herein, for use in the treatment of Syndrome X;

(ggg) An Active Ingredient for use in the control of obesity;

(hhh) An Active Ingredient for use in treating diabetes;

(iii) An Active Ingredient that is a PPAR receptor agonist;

(jjj) A compound of Formula I selected from the group consisting of

Racemic-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-5,6-dihydro-4H-cyclopentathiazol-4-ylmethylsulfanyl]-phenoxy}-acetic acid;

(R)-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-5,6-dihydro-4H-cyclopentathiazol-4-ylmethylsulfanyl]-phenoxy}-acetic acid;

(S)-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-5,6-dihydro-4H-cyclopentathiazol-4-ylmethylsulfanyl]-phenoxy}-acetic acid;

Racemic-3-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-5,6-dihydro-4H-cyclopentathiazol-4-ylmethoxy]-phenyl}-propionic acid;

Racemic-3-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-5,6-dihydro-4H-cyclopentathiazol-4-ylmethylsulfanyl]-phenyl}-propionic acid;

(R)-3-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-5,6-dihydro-4H-cyclopentathiazol-4-ylmethylsulfanyl]-phenyl}-propionic acid;

(S)-3-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-5,6-dihydro-4H-cyclopentathiazol-4-ylmethylsulfanyl]-phenyl}-propionic acid;

Racemic-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-benzothiazol-4-ylmethylsulfanyl]-phenoxy}-acetic acid;

(S)-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-benzothiazol-4-ylmethylsulfanyl]-phenoxy}-acetic acid;

(R)-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-benzothiazol-4-ylmethylsulfanyl]-phenoxy}-acetic acid;

{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-benzothiazol-4-ylmethoxy]-phenoxy}-acetic acid;

Racemic-3-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-benzothiazol-4-ylmethylsulfanyl]-phenyl}-propionic acid;

(R)-3-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-benzothiazol-4-ylmethylsulfanyl]-phenyl}-propionic acid;

(S)-3-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-benzothiazol-4-ylmethylsulfanyl]-phenyl}-propionic acid;

{3-[2-(4-Trifluoromethyl-phenyl)-5,6-dihydro-4H-cyclopentathiazol-4-ylmethoxy]-phenyl}-acetic acid;

(S)-{3-[2-(4-Trifluoromethyl-phenyl)-5,6-dihydro-4H-cyclopentathiazol-4-ylmethoxy]-phenyl}-acetic acid;

(R)-{3-[2-(4-Trifluoromethyl-phenyl)-5,6-dihydro-4H-cyclopentathiazol-4-ylmethoxy]-phenyl}-acetic acid;

{2-Methyl-4-[7-methyl-2-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-benzothiazol-4-ylmethylsulfanyl]-phenoxy}-acetic acid;

(S)-3-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-benzothiazol-4-ylmethoxy]-phenyl}-propionic acid;

(R)-3-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-benzothiazol-4-ylmethoxy]-phenyl}-propionic acid;

(R)-{3-[2-(4-Trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-benzothiazol-4-ylmethoxy]-phenyl}-acetic acid;

(S)-{3-[2-(4-Trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-benzothiazol-4-ylmethoxy]-phenyl}-acetic acid;
3-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-5,6,7,8-tetrahydro-4H-cycloheptathiazol-4-ylmethylsulfanyl]-phenyl}-propionic acid;
{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-5,6,7,8-tetrahydro-4H-cycloheptathiazol-4-ylmethylsulfanyl]-phenoxy}-acetic acid;
(R)-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-5,6,7,8-tetrahydro-4H-cycloheptathiazol-4-ylmethylsulfanyl]-phenoxy}-acetic acid;
(S)-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-5,6,7,8-tetrahydro-4H-cycloheptathiazol-4-ylmethylsulfanyl]-phenoxy}-acetic acid;
3-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-5,6,7,8-tetrahydro-4H-cycloheptathiazol-4-ylmethoxy]-phenyl}-propionic acid;
{3-[2-(4-Trifluoromethyl-phenyl)-5,6,7,8-tetrahydro-4H-cycloheptathiazol-4-ylmethoxy]-phenyl}-acetic acid;
(R)-3-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-5,6,7,8-tetrahydro-4H-cycloheptathiazol-4-ylmethylsulfanyl]-phenyl}-propionic acid;
(S)-3-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-5,6,7,8-tetrahydro-4H-cycloheptathiazol-4-ylmethylsulfanyl]-phenyl}-propionic acid;
{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-4,5,6,7,8,9-hexahydro-cyclooctathiazol-4-ylmethylsulfanyl]-phenoxy}-acetic acid;
{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-benzothiazol-4-ylmethylsulfanyl]-phenoxy}-acetic acid;
{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-benzothiazol-4-ylmethylsulfanyl]-phenoxy}-acetic acid ethyl ester;

3-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-benzothiazol-4-ylmethylsulfanyl]-phenyl}-propionic acid;
{3-[2-(4-Trifluoromethyl-phenyl)-benzothiazol-4-ylmethoxy]-phenyl}-acetic acid;
3-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-benzothiazol-4-ylmethoxy]-phenyl}-propionic acid;
(S)-2-Methoxy-3-{4-[2-(4-trifluoromethyl-phenyl)-benzothiazol-4-ylmethoxy]-phenyl}-propionic acid;
2-Methyl-2-{2-methyl-4-[2-(4-trifluoromethyl-phenyl)-benzothiazol-4-ylmethoxy]-phenoxy}-propionic acid;
Racemic-(2-methyl-4-{1-[2-(4-trifluoromethyl-phenyl)-benzothiazol-4-yl]-ethylsulfanyl}-phenoxy)-acetic acid; and
Racemic-3-(2-methyl-4-{1-[2-(4-trifluoromethyl-phenyl)-benzothiazol-4-yl]-ethylsulfanyl}-phenyl)-propionic acid;
and

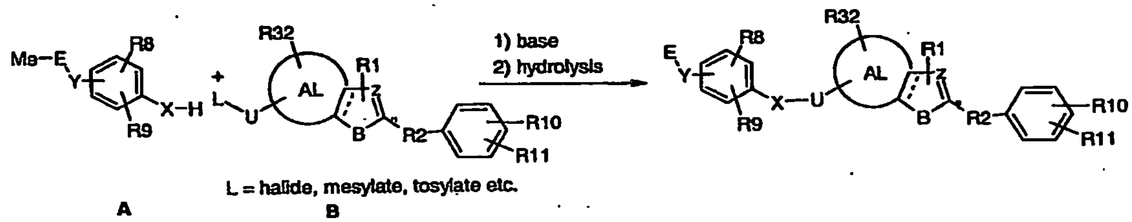
(kkk) A compound of Formula I selected from the group consisting of {2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-benzothiazol-4-ylmethylsulfanyl]-phenoxy}-acetic acid and 3-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-benzothiazol-4-ylmethylsulfanyl]-phenyl}-propionic acid.

SYNTHESIS

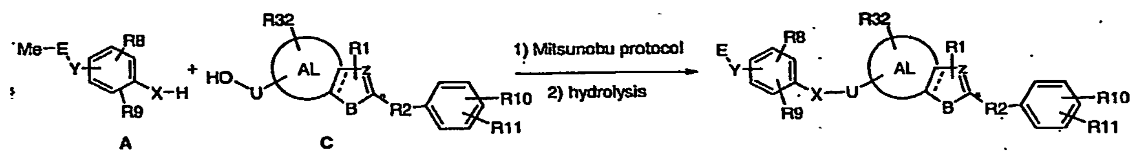
Compounds of the present invention have been formed as specifically described in the examples. Further, many compounds are prepared as more generally using a Mitsunobu protocol (O. Mitsunobu, 1981 Synthesis, p1) and other methods known to the skilled artisan. Alternative synthesis methods may also be effective and known to the skilled artisan.

For example, an intermediate like A is alkylated with an alkylating agent B in the presence of a base (e.g. K2CO3,

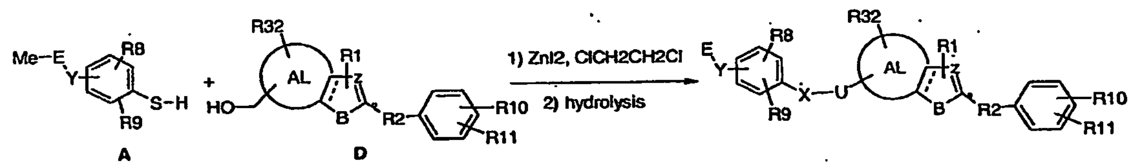
Cs2CO3 etc.). Hydrolysis in the presence of aqueous NaOH or LiOH gave the acid product.



Alternatively, an intermediate like A is coupled with an alcohol C under Mitsunobu reaction condition (DEAD/PPh3, ADDP/PBu3 etc.). Hydrolysis in the presence of aqueous NaOH or LiOH gave the acid product:

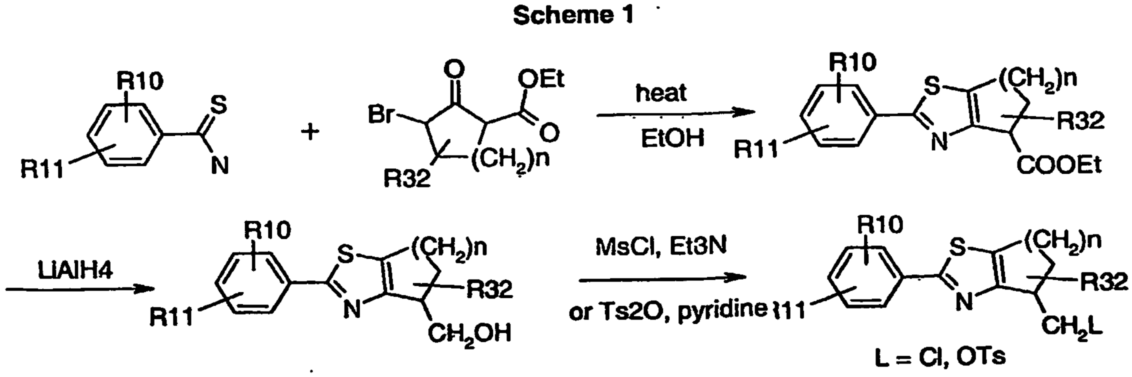


Thioether analogs could also be prepared by a ZnI2 mediated thioether formation reaction as shown below:



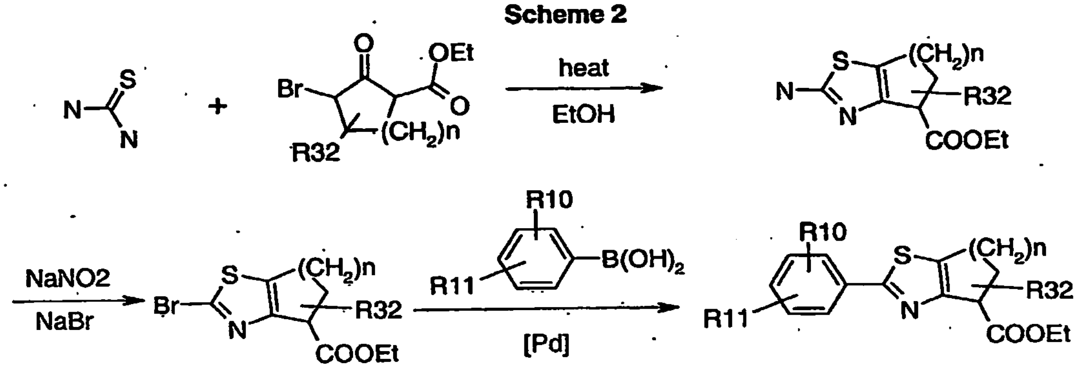
Intermediates B, C and D can be made in one of the following methods. Condensation α'-halo-β -ketoester with thioamide gave the thiazole compound:

Scheme 1

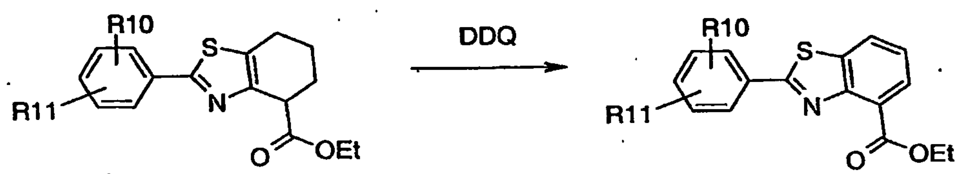


Alternatively, a convergent method was developed to make the variation at C2 position of the thiazole as shown in scheme 2:

Scheme 2



Benzothiazole analogs were made by DDQ oxidation reaction:



EXEMPLIFICATION

The Examples provided herein are illustrative of the invention claimed herein and are not intended to limit the scope of the claimed invention in any way.

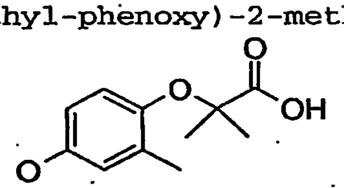
Instrumental Analysis

Infrared spectra are recorded on a Perkin Elmer 781 spectrometer. ^{1}H NMR spectra are recorded on a Varian 400 MHz spectrometer at ambient temperature. Data are reported as follows: chemical shift in ppm from internal standard tetramethylsilane on the δ scale, multiplicity (b = broad, s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet and m = multiplet), integration, coupling constant (Hz) and assignment. ^{13}C NMR are recorded on a Varian 400 MHz spectrometer at ambient temperature. Chemical shifts are reported in ppm from tetramethylsilane on the δ scale,

with the solvent resonance employed as the internal standard ($CDCl_3$ at 77.0 ppm and DMSO-d_6 at 39.5 ppm). Combustion analyses are performed by Eli Lilly & Company Microanalytical Laboratory. High resolution mass spectra are obtained on VG ZAB 3F or VG 70 SE spectrometers. Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light.

Preparation 1

2-(4-Hydroxy-2-methyl-phenoxy)-2-methyl-propionic acid



Step A

2-(4-Benzyloxy-2-formylphenoxy)-2-methyl propionic acid ethyl ester

5-Benzyloxy-2-hydroxy-benzaldehyde (Kappe, T.; Witoszynskyj, T. Arch. Pharm., 1975, 308 (5), 339-346) (2.28 g, 10.0 mmol), ethyl bromoisobutyrate (2.2 mL, 15 mmol), and cesium carbonate (3.26 g, 10.0 mmol) in dry DMF (25 mL) are heated at 80 °C for 18 h. The reaction mixture is cooled and partitioned between water (30 mL) and ether (75 mL). The organic layer is washed with brine (15 mL). The aqueous layers are back-extracted with ethyl acetate (30 mL), and the organic layer is washed with brine (20 mL). The combined organic layers are dried (Na_2SO_4) and concentrated to a brown oil. The crude product is purified by flash chromatography using hexanes:ethyl acetate (2.5:1) to give a pale yellow solid (3.04 g, 89%): mp 65 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, 3H, J = 7.1 Hz), 1.62 (s, 6H), 4.23 (q, 2H, J = 7.1 Hz), 6.81 (d, 1H, J = 8.8 Hz), 7.10 (dd, 1H, J = 4.6, 9.0 Hz), 7.30-7.43 (m, 6H); MS (ES) m/e 343.1 [M+1].

Step B

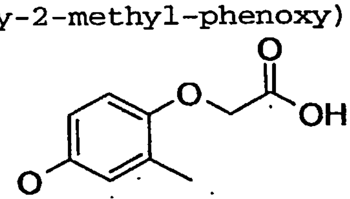
2-(4-Hydroxy-2-methyl-phenoxy)-2-methyl-propionic acid ethyl ester

2-(4-Benzyloxy-2-formyl-phenoxy)-2-methyl-propionic acid ethyl ester (9.00 g, 26.3 mmol) in ethanol (250 mL) is treated with 5% Pd/C (1.25 g) and hydrogen (60 psi, rt, overnight). Additional 5% Pd/C (1.25 g) is added, and the reaction is continued for 6h at 40 °C. The mixture is filtered and concentrated to a tan oil (6.25 g). This oil contained 9 mol% of 2-(4-Hydroxy-2-hydroxymethyl-phenoxy)-2-methyl-propionic acid ethyl ester. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, 3H, J = 7.3 Hz), 1.51 (s, 6H), 2.14 (s, 3H), 4.24 (q, 2H, J = 7.3 Hz), 5.68 (brs, 1H), 6.47 (dd, 1H, J = 3.4, 8.8 Hz), 6.59 (d, 1H, J = 8.3 Hz), 6.60 (brs, 1H).

The following compound is prepared in a similar manner:

Preparation 2

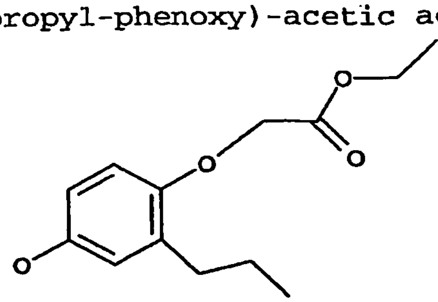
2-(4-Hydroxy-2-methyl-phenoxy)-acetic acid



^{1}H NMR (400 MHz, CDCl3) δ 1.28 (t, 3H, J = 7.1 Hz), 2.24 (s, 3H), 4.25 (q, 2H, J = 7.1 Hz), 4.55 (s, 2H), 6.56 (dd, 1H, J = 2.7, 8.5 Hz), 6.61 (d, 1H, J = 8.3 Hz), 6.65 (d, 2H, J = 2.9 Hz).

Preparation 3

(4-Hydroxy-2-propyl-phenoxy)-acetic acid ethyl ester



Step A

4-Benzyloxy-2-propylphenol

2-Allyl-4-benzyloxyphenol (WO 9728137 A1 19970807, Adams, A.D. et al.) (5.00 g, 20.8 mmol) in ethyl acetate (40 mL) is treated with 5% Pd/C (0.25 g) and hydrogen (1 atm) at ambient temperature for 18 h. The mixture is filtered and concentrated. The crude product is purified on a Biotage medium pressure chromatography system using a 40L normal phase cartridge and eluted with 10% ethyl acetate in hexanes to give a tan solid (2.8 g, 56%). Rf = 0.33 (25% EtOAc/Hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.31 (m, 5H), 6.78 (s, 1H), 6.69 (d, J = 1.5 Hz, 2H), 5.00 (s, 2H), 4.31 (s, 1H), 2.55 (t, J = 7.6 Hz, 2H), 1.64 (q, J = 7.5 Hz, 2H), 0.97 (t, J = 7.3 Hz, 3H).

Step B

(4-Benzyloxy-2-propylphenoxy)acetic acid ethyl ester

A solution of 4-benzyloxy-2-propylphenol (0.50 g, 1.94 mmol) in dry DMF (7 mL) is cooled in an ice bath and treated with NaH (0.15 g, 3.8 mmol, 60 % oil dispersion). The ice bath is removed, ethyl bromoacetate (0.43 mL, 3.9 mmol) is added, and the mixture is placed in an oil bath (T=85 °C). After 18 h, the reaction mixture is cooled and concentrated in vacuo. The residue is diluted with EtOAc, washed with brine (2x), dried (Na_2SO_4), and concentrated. The crude product is purified by radial chromatography using 10% ethyl acetate in hexanes to give a tan solid (0.62 g, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.31 (m, 5H), 6.82 (d, J = 2.9 Hz, 1H), 6.72 (dd, J = 8.8, 2.9 Hz, 1H), 6.66 (d, J = 8.8 Hz, 1H), 5.00 (s, 2H), 4.57 (s, 2H), 4.25 (q, J = 7.0 Hz, 2H), 2.63 (t, J = 7.6 Hz, 2H), 1.64 (q, J = 7.5 Hz, 2H), 1.29 (t, J = 7.1 Hz, 3H), 0.95 (t, J = 7.3 Hz, 3H); MS (FIA) m/e 329 (M+1).

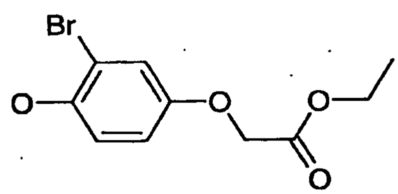
Step C

(4-Hydroxy-2-propylphenoxy)acetic acid ethyl ester

A solution of (4-benzyloxy-2-propylphenoxy)acetic acid ethyl ester (0.60 g, 1.83 mmol) in THF (15 mL) is treated with 5% Pd/C (75 mg) and hydrogen (60 psi) at ambient temperature for 24 h. The mixture is filtered and concentrated. The crude product is purified by radial chromatography using 15% ethyl acetate in hexanes to give a tan solid (0.25 g, 57%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.66 (d, J = 2.9 Hz, 1H), 6.62 (d, J = 8.8 Hz, 1H), 6.57 (dd, J = 8.8, 2.9 Hz, 1H), 4.56 (s, 1H), 4.40 (s, 1H), 4.25 (q, J = 7.2 Hz, 2H), 2.61 (t, J = 7.6 Hz, 2H), 1.63 (q, J = 7.5 Hz, 2H), 1.29 (t, J = 7.1 Hz, 3H), 0.95 (t, J = 7.3 Hz, 3H); MS (FIA) m/e 239 (M+1).

Preparation 4

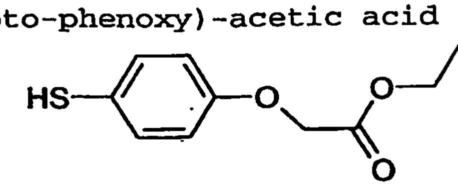
(3-Bromo-4-hydroxy-phenoxy)-acetic acid ethyl ester



To a solution of (4-hydroxy-phenoxy)-acetic acid ethyl ester (0.59 g, 3 mmol) in acetic acid (1.5 mL) is added bromine (0.48 g, 9 mmol) in acetic acid (0.5 mL) at room temperature. After 5 min, solvent is evaporated and purified by column chromatography on silica gel giving the title compound (0.6 g).

Preparation 5

(4-Mercapto-phenoxy)-acetic acid ethyl ester



Step A

(4-Chlorosulfonyl-phenoxy)-acetic acid ethyl ester

Phenoxy-acetic acid ethyl ester (9.1 mL) is added to chlorosulfonic acid (15 mL) at 0°C dropwise. The reaction is stirred at 0 °C for 30 min, it is allowed to warm to room temperature. After 2 hrs, the reaction mixture is poured into ice, solid product is collected by filtration and dried under vacuum.

Step B

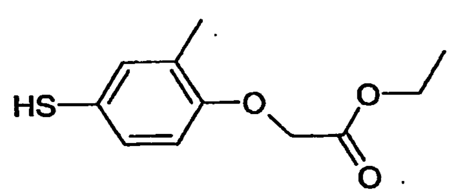
(4-Mercapto-phenoxy)-acetic acid ethyl ester

To a mixture of(4-chlorosulfonyl-phenoxy)-acetic acid ethyl ester (0.98 g, 3.5 mmol) and tin powder (2.1 g) in ethanol (4.4 mL) is added HCl in dioxane (1.0 M, 4.4 mL) under nitrogen. The mixture is heated to reflux for 2 hrs, it is poured into ice and methylene chloride and filtered. The layers are separated and extracted with methylene chloride, dried and concentrated. The crude product is used for next step without purification.

The following compounds are made in a similar manner:

Preparation 6

(4-Mercapto-2-methyl-phenoxy)-acetic acid ethyl ester



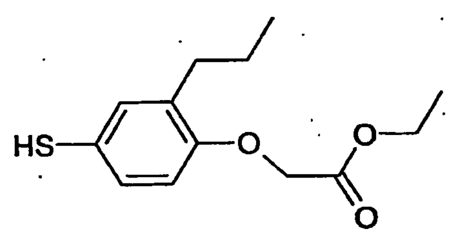
This compound can also be made by the following procedure: To a stirred suspension of Zn powder (10 µm, 78.16 g, 1.2 mol) and dichlorodimethyl silane (154.30 g, 145.02 mL, 1.2 mol) in 500 mL of dichloroethane is added a solution of (4-chlorosulfonyl-2-methyl-phenoxy)-acetic acid ethyl ester (100 g, .34 mol) and 1,3-dimethylimidazolidin-2-one (116.98 g, 112.05 mL, 1.02 mol) in 1L of DCE. Addition is at a rate so as to maintain the internal temperature at ~ 52 °C,

cooling with chilled water as necessary. After addition is complete, the mixture is heated at 75 °C for 1 hour. It is then cooled to room temperature, filtered and concentrated *iv*. Add MTBE, washed twice with saturated LiCl solution, concentrate *iv* again. Take up the residue in CH_3CN, wash with hexane (4X) and concentrate *iv* to yield a biphasic mixture. Let stand in a separatory funnel and separate layers, keeping the bottom layer for product. Filtration through a plug of silica gel (1 Kg, 25% EtOAc/hexane) and subsequent concentration yielded 61 g (79%) of a clear, colorless oil.

NMR (DMSO-d_6) δ 7.1 (s, 1H), 7.05 (dd, 1H), 6.75 (d, 1H), 5.03 (s, 1H), 4.75 (s, 2H), 4.15 (q, 2H), 2.15 (s, 3H), 1.2 (t, 3H).

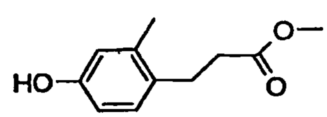
Preparation 7

(4-Mercapto-2-propyl-phenoxy)-acetic acid ethyl ester



Preparation 8

3-(4-Hydroxy-2-methyl-phenyl)-propionic acid methyl ester



Step A

4-Bromo-3-methyl-phenyl benzyl ester

To a solution of 4-Bromo-3-methyl-phenol (20.6 g, 0.0.11 mol) in DMF (100 mL) is added Cs2CO3 (54 g, 0.165 mol), followed by benzyl bromide (14.4 mL). After stirred at 60 °C for 40 h, the reaction mixture is diluted with ethyl acetate, filtered through celite. The filtrate is washed

with water and brine, dried over sodium sulfate, concentration gave the title product (27 g).

Step B

3-(4-Benzyloxy-2-methyl-phenyl)-propionic acid methyl ester

To a solution of 4-bromo-3-methyl-phenyl benzyl ester (7.6 g, 27.4 mmol) in propronitrile (200 mL) is added methyl acrylate (10 mL) and diisopropylethyl amine (9.75 mL), the solution is degassed and filled with nitrogen for three times. To this mixture are added tri-o-tolyl-phosphane (3.36 g) and palladium acetate (1.25 g) under nitrogen, then heated at 110 °C overnight, cooled to room temperature, filtered through celite. The solvent is evaporated, the residue is taken into ethyl acetate and washed with water and brine, dried over sodium sulfate. Concentration and column chromatography on silica gel eluted with hexanes and ethyl acetate gave the title compound (6.33 g).

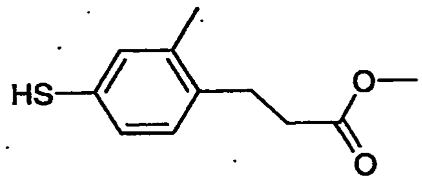
Step C

3-(4-Hydroxy-2-methyl-phenyl)-propionic acid methyl ester

A mixture of 3-(4-Benzyloxy-2-methyl-phenyl)-propionic acid methyl ester (13.7 g, 48.5 mmol) and Pd/C (5 %, 13.7 g) in MeOH (423 mL) is stirred under 60 psi of hydrogen for 24 hrs. Catalyst is filtered off, filtrate is concentrated giving the title compound (8.8 g, 93.5%).

Preparation 9

3-(4-Mercapto-2-methyl-phenyl)-propionic acid methyl ester



Step A

3-(4-Dimethylthiocarbamoyloxy-2-methyl-phenyl)-propionic acid methyl ester

3-(4-Hydroxy-2-methyl-phenyl)-propionic acid methyl ester (5.0 g, 25.75 mmol) is dissolved into dry dioxane (100 mL) and combined with 4-dimethylamino pyridine (0.500 g, 2.6 mmol), triethylamine (7.0 mL, 51.5 mmol), and dimethylaminothiocarbomoyl chloride (4.5 g, 32.17 mmol). The reaction is heated to reflux under nitrogen. The reaction is monitored by TLC until all of the phenol is consumed, 20h. After cooling to room temperature, the reaction is diluted with ethyl acetate (200 mL). Water (75 mL) is added and the two layers are separated. The organic layer is washed with brine (75mL) then dried over anhydrous sodium sulfate. The solvent is removed and the residue is dried under vacuum.

Step B

3-(4-Dimethylcarbamoylsulfanyl-2-methyl-phenyl)-propionic acid methyl ester

3-(4-Dimethylthiocarbamoyloxy-2-methyl-phenyl)-propionic acid methyl ester, taken crude from the previous step, is diluted with 75 mL of tetradecane and heated to reflux under nitrogen. The reaction is monitored by TLC until all the conversion is complete, 20h. The reaction is allowed to cool to room temperature, then the tetradecane is decanted

away from the resulting oil. The residue is rinsed several times with hexanes. This oil is then purified using flash column chromatography, yielding 5.01 g, or 69% (2 steps) of the product.

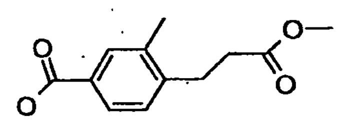
Step C

3-(4-Mercapto-2-methyl-phenyl)-propionic acid methyl ester

3-(4-Dimethylcarbamoylsulfanyl-2-methyl-phenyl)-propionic acid methyl ester (5.01 g, 17.8 mmol) is diluted with methanol (30 mL) and to this is added sodium methoxide (1.7 mL of 4M in methanol, 7.23 mmol). The reaction is heated to reflux under nitrogen and monitored by TLC. After complete conversion, 20h., the reaction is allowed to cool to room temperature. The reaction is neutralized with 1N HCl (7.23 mL) and diluted with ethyl acetate (150 mL). The two phases are separated and the organic layer is washed with water (75 mL), then brine (75 mL). The organic layer is then dried over anhydrous sodium sulfate, then concentrated to yield 4.43 g crude product that is used without further purification.

Preparation 10

4-(2-Methoxycarbonyl-ethyl)-3-methyl-benzoic acid



Step A

4-Bromo-3-methyl-benzoic acid benzyl ester

To a solution of 4-Bromo-3-methyl-benzoic acid benzyl (25.3 g, 0.118 mol) in DMF (200 mL) is added Cs2CO3 (76.6 g, 0.235 mol), followed by benzyl bromide (15.4 mL). After stirred at room temperature for 2 h, the reaction mixture is diluted with ethyl acetate, filtered through celite. The filtrate is washed with water and brine, dried over sodium sulfate, concentration gave the title product.

Step B

4-(2-Methoxycarbonyl-vinyl)-3-methyl-benzoic acid benzyl ester

To a solution of 4-bromo-3-methyl-benzoic acid benzyl ester (36 g, 118 mmol) in propronitrile (1000 mL) is added methyl acrylate (43.3 mL) and diisopropylethyl amine (42 mL), the solution is degassed and filled with nitrogen for three times. To this mixture are added tri-o-tolyl-phosphane (14.5 g) and palladium acetate (5.34 g) under nitrogen, then heated at 110 °C overnight, cooled to room temperature, filtered through celite. The solvent is evaporated, the residue is taken into ethyl acetate and washed with water and brine, dried over sodium sulfate. Concentration and column chromatography on silica gel eluted with hexanes and ethyl acetate gave the title compound (31 g, 84.7%).

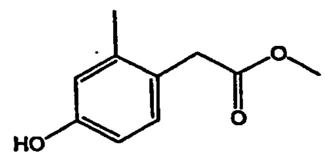
Step C

4-(2-Methoxycarbonyl-ethyl)-3-methyl-benzoic acid

A mixture of 4-(2-methoxycarbonyl-vinyl)-3-methyl-benzoic acid benzyl ester (11.6 g, 37.4 mmol) and Pd/C (5 %, 1.5 g) in THF (300 mL) and methanol (100 mL) is stirred under 60 psi of hydrogen overnight. Catalyst is filtered off, filtrate is concentrated giving the title compound (8.3 g, 100%).

Preparation 11

(4-Hydroxy-2-methyl-phenyl)-acetic acid methyl ester



Step A

4-Methoxy-2-methylbenzoic acid (2.5 g, 15.04 mmol) is stirred in thionyl chloride (50 mL) at reflux 2 hr. The mixture is concentrated and diluted with toluene (10 mL) and concentrated. The resulting solid is dried under vacuum 18 hr. The resulting acid chloride is stirred in 20 mL ether at 0 deg C. A solution of diazomethane (39.6 mmol) in ether (150 mL) is added to the acid chloride solution and stirred 18 hr. The resulting diazoketone solution is concentrated. The residue is stirred in methanol (100 mL) and a solution of silver benzoate in triethylamine (1.0 g in 10 mL) is added and the reaction is heated to 60 deg C and stirred 1 hr. The mixture is concentrated, diluted with 1.0 N aqueous hydrochloric acid (20 mL), extracted to three portions of ethyl acetate (50 mL each). The extracts are combined, washed with aqueous saturated sodium hydrogen carbonate, water, and brine (50 mL each), dried over anhydrous magnesium sulfate, filtered and concentrated. The residue is purified via silica gel chromatography eluting with 9:1 hexanes:ethyl acetate to afford 1.5 g (51%) of the homologated ester as a white solid.

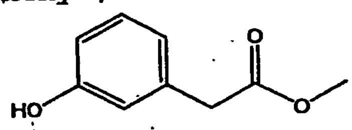
Step B

(4-Methoxy-2-methyl-phenyl)-acetic acid methyl ester (1.5 g, 7.72 mmol) is stirred in dichloromethane (50 mL) at 0 deg. C. Aluminum chloride (4.13 g, 31 mmol) is added followed by ethane thiol (2.9 mL, 38.6 mmol) . The resulting mixture is stirred at room temperature for 2 hr. Water (50 mL) is added and the product is extracted into ethyl acetate (3 X 50 ml), the extracts are combined, dried over anhydrous magnesium sulfate, filtered, and concentrated to afford the title compound as a colorless oil, 1.4 g,

100%. MS $M^{+}+1$ 181. The structure is confirmed by ^{1}H NMR spectroscopy.

Preparation 12

(3-Hydroxy-phenyl)-acetic acid methyl ester



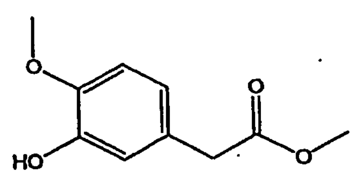
(3-Hydroxy-phenyl)-acetic acid methyl ester

(3-Hydroxy-phenyl)-acetic acid (5.0 g, 32.86 mmol) is stirred in methanol (100 mL) and concentrated (98%) sulfuric acid (3.0 mL,) is added. The mixture is heated to reflux 18 hr. The reaction is cooled and concentrated. The residue is diluted with water (100 mL) and extracted with ethyl acetate (3 X 50 mL). The combined extracts are dried over anhydrous magnesium sulfate, filtered, and concentrated to yield the title compound as an orange oil, 5.46 g, 100%. MS $M^{+}+1$ 167. The structure is confirmed by ^{1}H NMR spectroscopy.

The following compounds are made in a similar manner:

Preparation 13

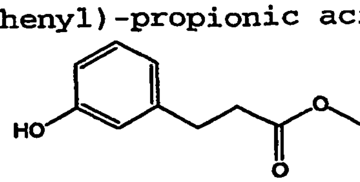
(3-Hydroxy-4-methoxy-phenyl)-acetic acid methyl ester



An orange oil. MS $M^{+}+1$ 197. The structure is confirmed by ^{1}H NMR spectroscopy.

Preparation 14

3-(3-Hydroxy-phenyl)-propionic acid methyl ester

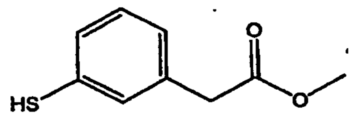


3-(3-Hydroxy-phenyl)-propionic acid methyl ester

An orange oil. MS M^{+}+1 181. The structure is confirmed by ^{1}H NMR spectroscopy.

Preparation 15

(3-Mercapto-phenyl)-acetic acid methyl ester



Step A

(3-Dimethylthiocarbamoyloxy-phenyl)-acetic acid methyl ester

A mixture of (3-Hydroxy-phenyl)-acetic acid methyl ester (5.5 g, 33.1 mmol) , N,N-dimethyl thiocarbamoyl chloride (5.11 g, 41.38 mmol), triethylamine (9.2 mL, 66.2 mmol), N,N-dimethylamino pyridine (0.4 g, 3.31 mmol) and dioxane (50 mL) is stirred at reflux 18 hr. The mixture is concentrated, partioned between 1M aqueous hydrochloric acid (200 mL) and ethyl acetate (3 X 75 mL). The combined organic extracts are dried over anhydrous magnesium sulfate, filtered, concentrated, and purified via silica chromatography eluting the product with dichloromethane to afford the title compound as a brown oil, 6.8 g, 81%. MS M^{+}+1 254. The structure is confirmed by ^{1}H NMR spectroscopy.

Step B

<u>(3-Dimethylcarbamoylsulfanyl-phenyl)-acetic acid methyl ester</u>

(3-Dimethylthiocarbamoyloxy-phenyl)-acetic acid methyl ester (6.8 g, 26.84 mmol) is stirred in tetradecane (30 mL) at 255 deg C for 8 hr. The mixture is cooled, the residue is purified by silica chromatography eluting the product with hexanes to 1:1 hexanes:ethyl acetate to afford the title compound as an orange oil, 4.9 g, 58 %. MS M^{+}+1 254. The structure is confirmed by ^{1}H NMR spectroscopy.

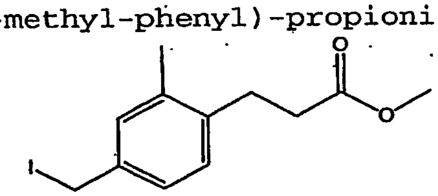
Step C

(3-Mercapto-phenyl)-acetic acid methyl ester

A mixture of (3-dimethylcarbamoylsulfanyl-phenyl)-acetic acid methyl ester (2.0 g, 7.9 mmol), potassium hydroxide (1.4 g, 24 mmol) methanol (50 mL), and water (5 mL) is stirred at reflux 3 hr. The mixture is concentrated, and product partitioned between 1M aqueous hydrochloric acid (50 mL) and ethyl acetate (3 X 75 mL). The combined extracts are dried over anhydrous magnesium sulfate, filtered and concentrated. The residue is taken up in methanol (50 mL), 2 mL concentrated sulfuric acid is added, and the mixture refluxed 3 hr. The mixture is concentrated, and the residue purified by silica chromatography eluting with 7:3 hexanes:ethyl acetate to afford the title compound as a pale yellow oil, 1.0 g, 69%. MS M^{+}+1 183. The structure is confirmed by ^{1}H NMR spectroscopy.

Preparation 16

3-(4-Iodomethyl-2-methyl-phenyl)-propionic acid methyl ester



Step A

3-(4-Hydroxymethyl-2-methyl-phenyl)-acrylic acid methyl ester

A mixture of methyl-4-bromo-3-methylbenzoate (5.7 g, 24.88 mmol), lithium aluminum hydride (29 mL, 29 mmol, 1 M solution in tetrahydrofuran) and tetrahydrofuran (100 mL) is stirred in ice/water for 1 hr. The reaction is quenched with aqueous hydrochloric acid (50 mL, 1 M). The product is extracted into ethyl acetate (3 X 100 mL). The combined extracts are dried over anhydrous magnesium sulfate, filtered and concentrated. The crude product is taken up in propionitrile (100 mL). Methylacrylate (10 mL, 121.5 mmol),

palladium acetate (1.12 g, 5 mmol), tri-o-tolylphosphine (3.0 g, 10 mmol), and N,N-diisopropyl ethylamine (8.7 mL, 50 mmol) are sequentially added and the resulting reaction mixture is heated to 110 deg C 3 hr. The mixture is concentrated, and the residue diluted with aqueous hydrochloric acid (100 mL, 1M).The product is extracted with dichloromethane (2 X 100 mL) and ethyl acetate (100 mL). The combined extracts are dried over anhydrous magnesium sulfate, filtered, concentrated, and purified via silica chromatography eluting with 7:3 hexanes:ethyl acetate to 1:1 hexanes:ethyl acetate to afford the pure product as a yellow oil, 4.7 g, 91 %. MS M^{+}+1 207. The structure is confirmed by ^{1}H NMR spectroscopy.

Step B

3-(4-Hydroxymethyl-2-methyl-phenyl)-propionic acid methyl ester

A mixture of 3-(4-Hydroxymethyl-2-methyl-phenyl)-acrylic acid methyl ester (4.7 g, 22.8 mmol), Raney nickel (0.668 g) and tetrahydrofuran (618 mL) is shaken under 60 psig. Hydrogen 24 hr. The catalyst is filtered off, and the mixture is concentrated to afford the product as a pale yellow oil, 4.3 g, 91%. The structure is confirmed by ^{1}H NMR spectroscopy.

Step C

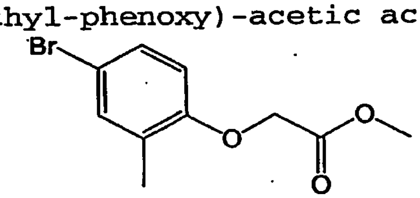
3-(4-Iodomethyl-2-methyl-phenyl)-propionic acid methyl ester

A mixture of 3-(4-Hydroxymethyl-2-methyl-phenyl)-propionic acid methyl ester (0.62 g, 2.98 mmol), triphenyl phosphine (0.86 g, 3.27 mmol) and dichloromethane (10 mL) is stirred at room temperature. A solution of iodine (0.83 g, 3.27 mmol) in benzene (5 mL) is added and the black mixture is stirred at room temperature 2hr. The brown mixture is diluted with 10% aqueous sodium hydrogen sulfite (5 mL) and the resulting clear mixture is washed with ethyl acetate (3

X 50 mL). The combined extracts are dried over anhydrous magnesium sulfate, filtered and concentrated. The residue is purified via silica chromatography eluting with 9:1 hexanes:ethyl acetate to afford the title compound as a crystalline ivory solid, 0.68g, 72%. MS M^{+}+1 319. The structure is confirmed by ^{1}H NMR spectroscopy.

Preparation 17

(4-Bromo-2-methyl-phenoxy)-acetic acid methyl ester



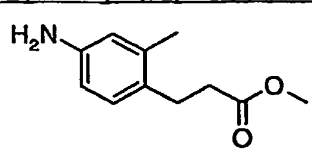
Step A

(4-Bromo-2-methyl-phenoxy)-acetic acid methyl ester

A mixture of 4-bromo-2-methylphenol (1.0 g, 5.35 mmol), sodium hydride (0.26 g, 6.42 mmol, 60% mineral oil), N,N-dimethylformamide (10 mL), and methyl-2-bromoacetate (0.56 mL, 5.88 mmol) is stirred at room temperature 18 hr. The mixture is diluted with water (50 mL) and the product extracted to ethyl acetate (3 X 50 mL). The combined extracts are dried over anhydrous magnesium sulfate, filtered, concentrated and purified via silica chromatography eluting with 8:2 hexanes:ethyl acetate to afford title compound as a colorless oil, 1.03 g, 74%. MS M^{+} 259. The structure is confirmed by ^{1}H NMR spectroscopy.

Preparation 18

3-(4-Amino-2-methyl-phenyl)-propionic acid methyl ester



Step A

3-(2-Methyl-4-nitro-phenyl)-acrylic acid methyl ester

To a solution of 2-bromo-5-nitrotoluene (3.11 g, 14.39 mmol) in propionitrile (105 mL) is added DIPEA (5.1 mL, 29.28

mmol). The mixture is degassed three times. Methyl acrylate (5.2 mL, 57.74 mmol) is added and the mixture is degassed. Tri-*o*-tolylphosphine (1.77 g, 5.82 mmol) and $Pd(OAc)_2$ (0.64 g, 2.85 mmol) are added and the mixture is degassed a final two times followed by heating at 110°C for 4 h. Upon cooling, the mixture is passed through Celite and the filtrate is concentrated. The residue is partitioned between Et_2O and 1N HCl. The organics are washed with saturated $NaHCO_3$ and brine, and dried with Na_2SO_4. The crude material is purified by flash chromatography to yield the title compound (2.90 g, 91%).

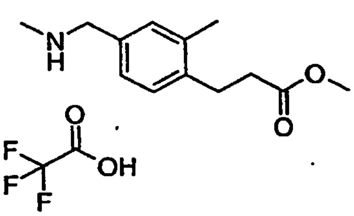
Step B

3-(4-Amino-2-methyl-phenyl)-propionic acid methyl ester

A mixture of 3-(2-Methyl-4-nitro-phenyl)-acrylic acid methyl ester (1.47 g, 6.64 mmol) and 5% Pd/C (0.29 g) in MeOH (100 mL) is exposed to a hydrogen atmosphere (60 psi) for 12 h. The mixture is filtered through Celite and purified by flash chromatography to yield the title compound (0.99 g, 77%).

Preparation 19

3-(2-Methyl-4-methylaminomethyl-phenyl)-propionic acid methyl ester TFA salt



Step A

3-(4-Formyl-2-methyl-phenyl)-propionic acid methyl ester

A mixture of 3-(4-Hydroxymethyl-2-methyl-phenyl)-propionic acid methyl ester (0.49 g, 2.35 mmol) and MnO_2 (0.80 g, 9.20 mmol) in chloroform (5 mL) is stirred at RT for 4 days. The mixture is filtered through Celite; the Celite is washed with copious amounts of EtOAc. The filtrate is concentrated

and purified by flash chromatography to yield the title compound (0.29 g, 60%).

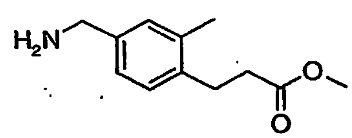
Step B

<u>3-(2-Methyl-4-methylaminomethyl-phenyl)-propionic acid methyl ester trifluoroacetic acid</u>

To a mixture of 3-(4-Formyl-2-methyl-phenyl)-propionic acid methyl ester (0.27 g, 1.31 mmol) and methylamine (2M in THF, 0.60 mL, 1.20 mmol) in anhydrous CH_2Cl_2 (10 mL) is added 4Å molecular sieves followed by acetic acid (0.090 mL, 1.57 mmol). The mixture is stirred at RT for 1.5 h. Sodium triacetoxyborohydride (0.39 g, 1.85 mmol) is added, and the mixture is stirred overnight. The reaction is quenched with saturated $NaHCO_3$. The organics are washed with saturated $NaHCO_3$ and brine, and dried with $MgSO_4$. Upon concentration, the mixture is purified by reverse phase chromatography to yield the title compound (0.12 g, 45%).

Preparation 20

<u>3-(4-Aminomethyl-2-methyl-phenyl)-propionic acid methyl ester</u>



Step A

<u>3-(4-Chloromethyl-2-methyl-phenyl)-propionic acid methyl ester</u>

To a 0°C solution of 3-(4-Hydroxymethyl-2-methyl-phenyl)-propionic acid methyl ester (1.02 g, 4.90 mmol) in anhydrous CH_2Cl_2 (15 mL) is added triethylamine (0.75 mL, 5.38 mmol) followed by thionyl chloride (0.40 mL, 5.48 mmol). The mixture is allowed to warm to RT overnight. Water is added, and the mixture is extracted with CH_2Cl_2. The organics are dried with $MgSO_4$ and concentrated. The crude material is purified by flash chromatography to yield the title compound (1.01 g, 91%).

Step B

3-(4-Azidomethyl-2-methyl-phenyl)-propionic acid methyl ester

To a solution of 3-(4-Chloromethyl-2-methyl-phenyl)-propionic acid methyl ester (0.52 g, 2.31 mmol) in DMF (7 mL) is added sodium azide (0.25 g, 3.84 mmol). The mixture is stirred overnight. Water is added, and the mixture is extracted with EtOAc. The organics are dried with Na_2SO_4 and concentrated to yield the title compound (0.49 g, 91%). The material is used without further purification.

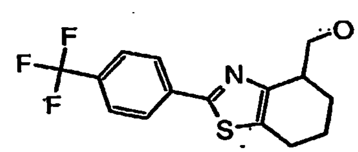
Step C

3-(4-Aminomethyl-2-methyl-phenyl)-propionic acid methyl ester

A mixture of 3-(4-Azidomethyl-2-methyl-phenyl)-propionic acid methyl ester (0.20 g, 0.86 mmol) and 5% Pd/C (32 mg) in EtOH (50 mL) is exposed to a hydrogen atmosphere (60 psi) at RT overnight. Upon filtering the mixture through Celite, the filtrate is concentrated to yield the title compound (0.14 g, 78%). The material is used without further purification.

Preparation 22

[2-(4-Trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-benzothiazol-4-yl]-methanol



Step A

A solution of bromine (0.2056 mol, 32.85 g) in anhydrous dichloromethane (50 mL) is added dropwise over 2h. to a solution of 2-oxo-cyclohexanecarboxylic acid ethyl ester (0.2056 mol, 35 g)in dichloromethane (200 mL) at 0°C-5°C. After the addition, the mixture is allowed to stir 0.5h. at 0°C, then the ice bath is removed and the mixture is allowed

to stir at room temperature for 18h. The reaction is monitored by TLC and HPLC until complete consumtion of starting material, then ice water (200 mL) is added with stirring. The organic layer is collected and washed twice with ice water (200 mL), twice with 200 mL of 10% aqueous sodium thiosulfate, and 200 mL of brine. The filtered solution is dried over anhydrous sodium sulfate, then concentrated to a clear liquid, 0.189 mol, 47 g. 92% yield. *Actually a mix of methyl/ethyl ester due to impure starting ester(10% methyl ester)

Step B

4-trifluoromethyl-thiobenzamide(48.7 mmol, 10 g) is dissolved in denatured ethanol (200 mL) and 3-bromo-2-oxo-cyclohexanecarboxylic acid ethyl ester (12.4 g, 50 mmol) is added, then the reaction is heated under nitrogen to reflux. The reaction is monitored by TLC and HPLC to complete consumption of the thioamide, and then allowed to cool. The cooled reaction is concentrated and diluted with 250 mL ethyl acetate. The residue is washed with 100 mL saturated sodium bicarbonate followed by water and brine. The organic layer is dried over anhydrous sodium sulfate, then concentrated and purified by column chromatrography. The fractions that contained pure product are concentrated to yield 5.06 g (30.6%) ester as a solid.

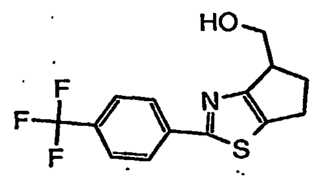
Step CTHF (50 mL) solution of 2-(4-Trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-benzothiazole-4-carboxylic acid ethyl ester (4.13 g, 11.6 mmol) is cooled to 0 °C and a 1M $LiAlH_4$ (11.6 mL, 11.6 mmol) is added slowly. The reaction is warmed to room temperature slowly, after stirring at room temperature for 2 h, tlc (15% EtOAc/hexane) showed that all the starting ester had been consumed. The reaction is cooled and carefully quenched with 2.4 mL water, 2.4 mL 5N NaOH and 7 mL water. The light tan solid is filter through celite and dried to give crude product (2.74 g, 8.74 mmol). The racemic alcohol [2-(4-Trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-benzothiazol-4-yl]-methanol is resolved on a

Chiralpak AD column (4.6 x 250 mm). Eluted with ethanol in heptane(9:1) and concentrated the fractions to provide pure enantiomer alcohols (isomer 1, 100% ee and isomer 2, 98.2% ee).

The following compounds are obtained in a substantially similar procedure:

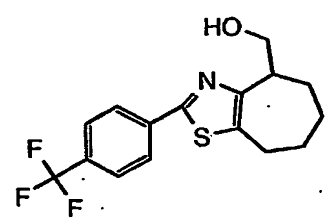
Preparation 23

[2-(4-Trifluoromethyl-phenyl)-5,6-dihydro-4H-cyclopentathiazol-4-yl]-methanol



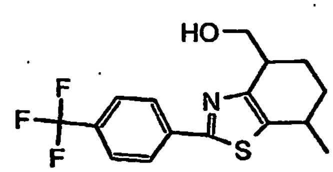
Preparation 24

[2-(4-Trifluoromethyl-phenyl)-5,6,7,8-tetrahydro-4H-cycloheptathiazol-4-yl]-methanol



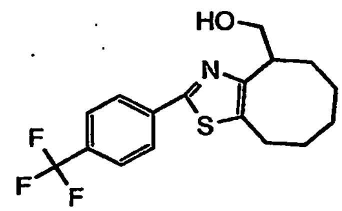
Preparation 25

[7-Methyl-2-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-benzothiazol-4-yl]-methanol



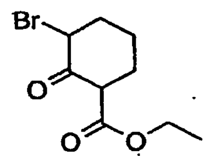
Preparation 26

[2-(4-Trifluoromethyl-phenyl)-4,5,6,7,8,9-hexahydro-cyclooctathiazol-4-yl]-methanol



Preparation 27

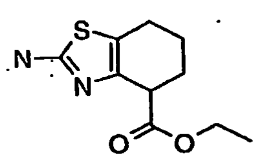
3-Bromo-2-oxo-cyclohexanecarboxylic acid ethyl ester



To a solution of 2-oxo-cyclohexanecarboxylic acid ethyl ester (30 g, 0.176 mol) in ether is added bromine (29.6 g, 0.185 mol) dropwise at room temperature, then stirred at room temperature for 2 h. The reaction mixture is quenched by water, and layers are separated. Organic layer is washed with Na2S2O4 and brine, dried over sodium sulfate. Concentration under vacuum gave the title compound, which is used for next step without further purification.

Preparation 28

2-Amino-4,5,6,7-tetrahydro-benzothiazole-4-carboxylic acid ethyl ester

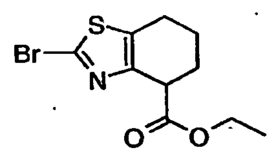


To a solution of thiourine (15 g, 0.197 mol) in ethanol (400 mL) is added 3-Bromo-2-oxo-cyclohexanecarboxylic acid ethyl ester (44.7 g, 0.179 mol) dropwise. After stirred at room

temperature for 2 days, the reaction mixture is poured into ice, basified with 5N NaOH. Solid is formed when the mixture is basic. Filtration gave a solid product, dried under vacuum (37 g, 91.3 % yield).

Preparation 29

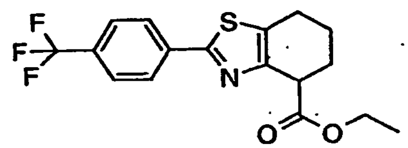
2-Bromo-4,5,6,7-tetrahydro-benzothiazole-4-carboxylic acid ethyl ester



To a solution of $CuSO_4$ 11.6g, 72.7 mmol) and sulfuric acid (139 mL) in water (324 mL) is added 2-Amino-4,5,6,7-tetrahydro-benzothiazole-4-carboxylic acid ethyl ester (11.3 g, 50 mmol) and a solution of sodium bromide (10.3 g, 100 mmol) in water (46 mL) at -10 oC. Then a solution of sodium nitrite (6 g, 87 mmol) in water (46 mL) is added beneath the reaction mixture surface via a TFE tubing connected at the tip of the additional funnel. After addition, the reaction mixture is warmed to room temperature. The reaction mixture is extracted with ether, combined organic layers are washed with water and brine, dried over sodium sulfate. Column chromatography on silica gel gave the title compound (4.8g, 33.1% yield).

Preparation 30

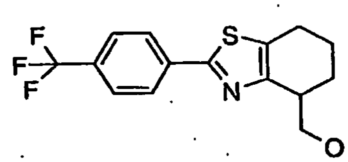
2-(4-Trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-benzothiazole-4-carboxylic acid ethyl ester



A mixture of 2-Bromo-4,5,6,7-tetrahydro-benzothiazole-4-carboxylic acid ethyl ester (3.5 g, 12.1 mmol) and 4-trifluoromethylphenyl boronic acid (2.52 g, 13.3 mmol) and CsF (6.44 g, 42.4 mmol) in dioxane (40 mL) is degassed and filled with nitrogen for three times, then PdCl2(dppf) (0.6 g, 0.7 mmol) is added under nitrogen. The reaction mixture is heated to reflux. After 40 hrs, the reaction mixture is cooled to room temperature, filtered through celite, concentrated and purified on silica gel (Hexane/ethyl acetate as eluent) giving 2.85 g of the title compound.

Preparation 31

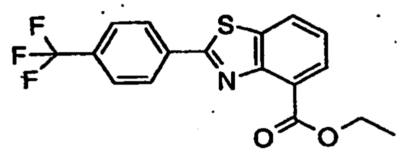
[2-(4-Trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-benzothiazol-4-yl]-methanol



To a solution of 2-(4-Trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-benzothiazole-4-carboxylic acid ethyl ester (5.27 g, 14.8 mmol) in THF (50 mL) is added LiAlH4 (1.0 M in THF, 16 mL, 16 mmol) at 0~5 °C. After stirred for 4 hrs, quenched by water and NaOH (5.0 N, 1 mL), diluted with ether, filtered through celite. Concentration and column chromatography on silica gel gave the title compound (4.4 g, 94.9 % yield).

Preparation 32

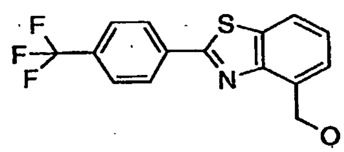
2-(4-Trifluoromethyl-phenyl)-benzothiazole-4-carboxylic acid ethyl ester



To a solution of 2-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-benzothiazole-4-carboxylic acid ethyl ester (2.74 g, 7.71 mmol) in chlorobenzene (100 mL) is added DDQ (5.25 g, 23.1 mmol), then the mixture is refluxed for 3 hr, cooled to room temperature. The reaction mixture is loaded on 70 gram of SAX columns, which are pretreated with NaHCO3 aq, followed by water and and methanol. The SAX column is eluted with acetone, concentration of the filtrate gave the title compound (2.70 g).

Preparation 33

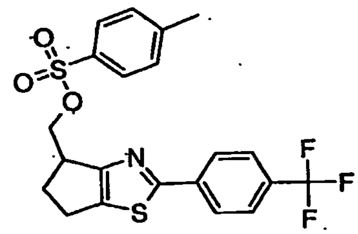
[2-(4-Trifluoromethyl-phenyl)-benzothiazol-4-yl]-methanol



To a solution of 2-(4-trifluoromethyl-phenyl)-benzothiazole-4-carboxylic acid ethyl ester (2.8 g, 8.0 mmol) in THF (8 mL) is added LiAlH4 (1.0 M in THF, 8 mL, 8 mmol) at 0~5 °C. After stirred for 4 hrs, quenched by water and NaOH (5.0 N, 1 mL), diluted with ether, filtered through celite. Concentration and column chromatography on silica gel gave the title compound.

Preparation 34

Toluene-4-sulfonic acid 2-(4-trifluoromethyl-phenyl)-5,6-dihydro-4H-cyclopentathiazol-4-ylmethyl ester



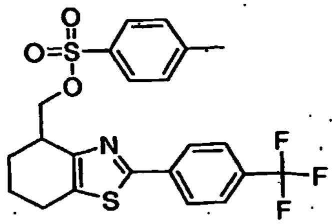
General procedure for the tosylate formation:

To a solution of alcohol (9.60 mmol) in anhydrous dichloromethane (50 mL) is added 4-N,N-dimethylamino pyridine (0.500 g, 4.00 mmol), tosic anhydride (8.4 g, 24 mmol), and pyridine (3.4 mL, 42 mmol) at room temperature. The reaction is monitored by TLC, and upon complete consumption of the starting alcohol, the reaction is diluted with DCM and extracted against saturated sodium bicarbonate solution. The organic layer is washed with water and brine, then dried over anhydrous sodium sulfate and concentrated. The pure tosylate product is obtained after flash column chromatography.

The following compound is made in a similar manner:

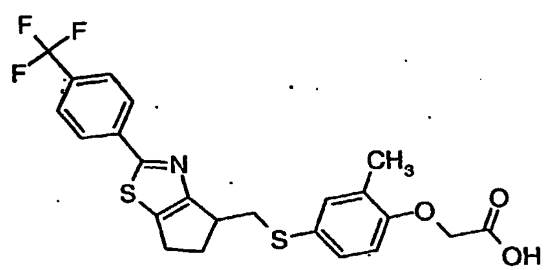
Preparation 35

Toluene-4-sulfonic acid 2-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-benzothiazol-4-ylmethyl ester



Example 1

Racemic-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-5,6-dihydro-4H-cyclopentathiazol-4-ylmethylsulfanyl]-phenoxy}-acetic acid



Step 1

(4-mercapto-2-methyl-phenoxy)-acetic acide methyl ester (109 mg, 0.500 mmol) is dissolved into anhydrous acetonitrile(ACN) (2 mL). Racemic-toluene-4-sulfonic acid 2-(4-trifluoromethyl-phenyl)-5,6-dihydro-4H-cyclopentathiazol-4-ylmethyl ester (206 mg, 0.495 mmol) is added to the reaction, followed by the addition of cesium carbonate (326 mg, 1.00 mmol). The reaction is allowed to stir under nitrogen at room temperature and monitored by TLC and HPLC. Upon complete consumption of the tosylate, the reaction is diluted with diethyl ether and quenched with 0.1N NaOH. The two phases are separated, then the organic layer washed with water and brine. The organic phase is dried over anhydrous sodium sulfate and concentrated under vacuum. The residue is further purified using either EtOAc/Hexanes(1:9) or Acetone/Hexanes(1:9) gradients on silica gel chromatography to yield {2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-5,6-dihydro-4H-cyclopentathiazol-4-

ylmethylsulfanyl]-phenoxy}-acetic acid ethyl ester (110 mg, 0.228 mmol) or 45%.

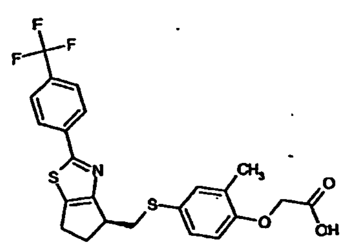
Step 2

{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-5,6-dihydro-4H-cyclopentathiazol-4-ylmethylsulfanyl]-phenoxy}-acetic acid ethyl ester (110 mg, 0.228 mmol) is dissolved in tetrahydrofuran (1mL) and 1N LiOH (1mL) is added. The mixture is heated to reflux until the conversion is complete. Upon complete conversion, the reaction is cooled to room temperature and 1N HCl (1mL) is added. The mixture is diluted with diethyl ether and extracted with 1N HCl. The organic layer is washed with water and brine, then dried over anhydrous sodium sulfate. Concentration of the solvent reveals the pure {2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-5,6-dihydro-4H-cyclopentathiazol-4-ylmethylsulfanyl]-phenoxy}-acetic acid (108 mg, 0.225 mmol) in near quantitative yield.

The following compounds are made in a substantially similar manner:

Example 2

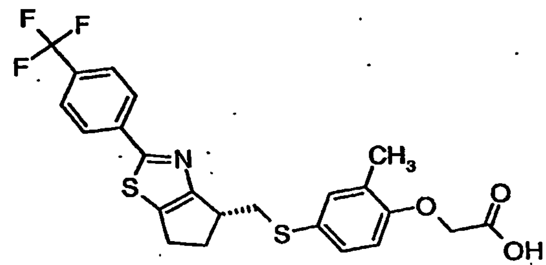
<u>(R)-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-5,6-dihydro-4H-cyclopentathiazol-4-ylmethylsulfanyl]-phenoxy}-acetic acid</u>



MS (ES): 480.44(M^{+}+1).

Example 3

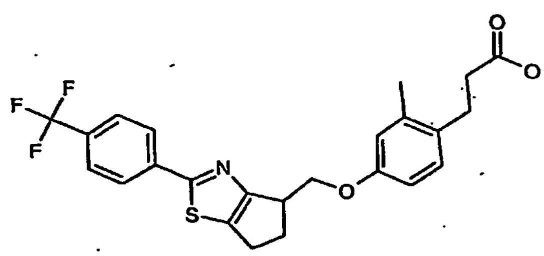
(S)-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-5,6-dihydro-4H-cyclopentathiazol-4-ylmethylsulfanyl]-phenoxy}-acetic acid



MS (ES): 480.44(M^{+}+1).

Example 4

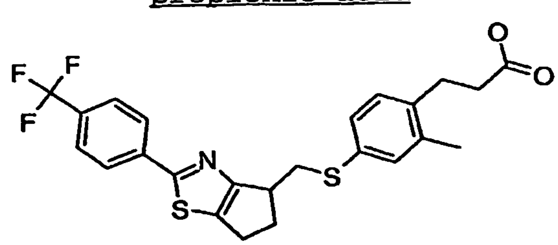
Racemic-3-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-5,6-dihydro-4H-cyclopentathiazol-4-ylmethoxy]-phenyl}-propionic acid



MS (ES): 484.2(M^{+}+1).

Example 5

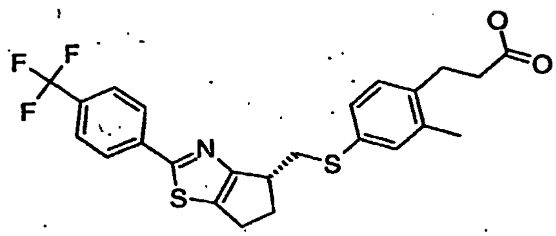
Racemic-3-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-5,6-dihydro-4H-cyclopentathiazol-4-ylmethylsulfanyl]-phenyl}-propionic acid



MS (ES): 478.24(M^{+}+1).

Example 6

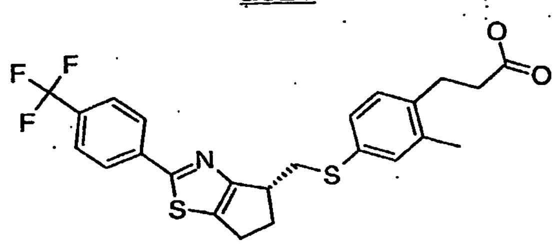
(R)-3-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-5,6-dihydro-4H-cyclopentathiazol-4-ylmethylsulfanyl]-phenyl}-propionic acid



MS (ES): 478.15(M^{+}+1).

Example 7

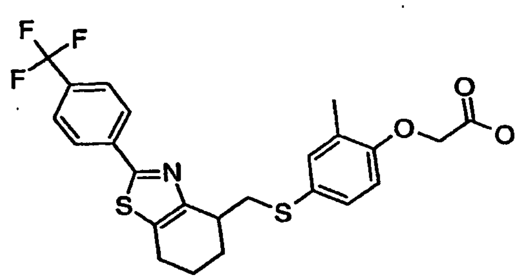
(S)-3-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-5,6-dihydro-4H-cyclopentathiazol-4-ylmethylsulfanyl]-phenyl}-propionic acid



MS (ES): 478.15(M^{+}+1).

Example 8

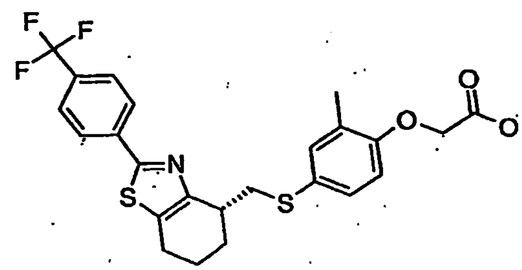
Racemic-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-benzothiazol-4-ylmethylsulfanyl]-phenoxy}-acetic acid



MS (ES): 494.2(M^{+}+1).

Example 9

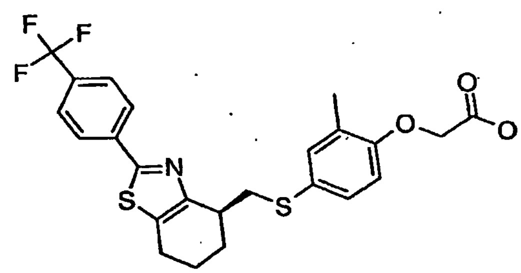
(S)-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-benzothiazol-4-ylmethylsulfanyl]-phenoxy}-acetic acid



MS (ES): 494.0(M^{+}+1).

Example 10

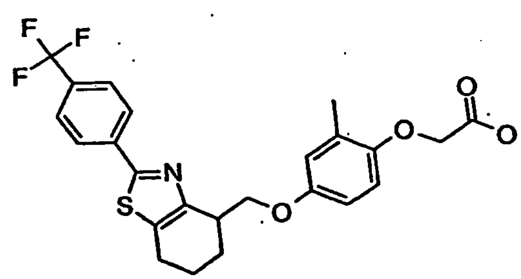
(R)-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-benzothiazol-4-ylmethylsulfanyl]-phenoxy}-acetic acid



MS (ES): 494.0(M^{+}+1).

Example 11

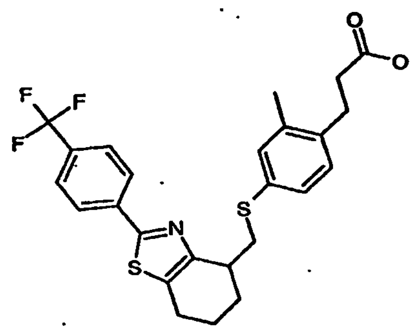
{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-benzothiazol-4-ylmethoxy]-phenoxy}-acetic acid



MS (ES): 478.2(M^{+}+1).

Example 12

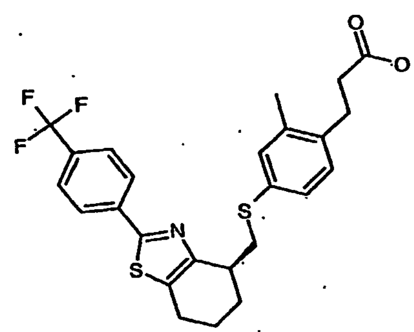
Racemic-3-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-benzothiazol-4-ylmethylsulfanyl]-phenyl}-propionic acid



MS (ES): 492.25(M^{+}+1).

Example 13

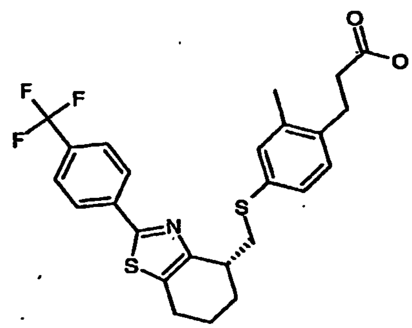
(R)-3-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-benzothiazol-4-ylmethylsulfanyl]-phenyl}-propionic acid



MS (ES): 492.13(M^{+}+1).

Example 14

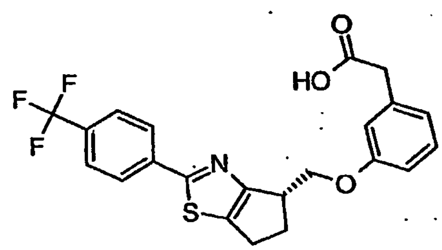
(S)-3-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-benzothiazol-4-ylmethylsulfanyl]-phenyl}-propionic acid



MS (ES): 492.14(M^{+}+1).

Example 15

{3-[2-(4-Trifluoromethyl-phenyl)-5,6-dihydro-4H-cyclopentathiazol-4-ylmethoxy]-phenyl}-acetic acid



Step 1

[2-(4-Trifluoromethyl-phenyl)-5,6-dihydro-4H-cyclopentathiazol-4-yl]-methanol (299 mg, 1.0 mmol) is dissolved into anhydrous toluene (5 mL) and cooled in an ice bath to 0°C with stirring under nitrogen. Tributyl phosphine (400 uL, 1.50 mmol) is added by syringe followed by 1-1'-azodicarbonyl-dipiperidine (405 mg, 1.50 mmol). Finally, (3-Hydroxy-phenyl)-acetic acid methyl ester (208 mg, 1.25 mmol) is then added. The reaction is allowed to stir under nitrogen at 0°C for 1 hour, then room temperature and monitored by TLC and HPLC. Upon completion, the reaction is diluted with hexanes and allowed to stir vigorously for 10 min. The resulting white precipitate is then filtered away and the solution is concentrated under vacuum. The residue is further purified using either EtOAc/Hexanes(1:9) or Acetone/Hexanes(1:9) gradients on silica gel chromatography to yield {3-[2-(4-Trifluoromethyl-phenyl)-5,6-dihydro-4H-cyclopentathiazol-4-ylmethoxy]-

phenyl}-acetic acid methyl ester (179 mg, 0.400 mmol) or 40%.

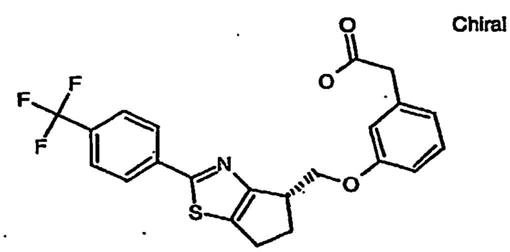
Step 2

{3-[2-(4-Trifluoromethyl-phenyl)-5,6-dihydro-4H-cyclopentathiazol-4-ylmethoxy]-phenyl}-acetic acidmethyl ester (179 mg, 0.400 mmol) is dissolved in tetrahydrofuran (1mL) and 5N NaOH (1mL) is added. The mixture is heated to reflux until the conversion is complete. Upon complete conversion, the reaction is cooled to room temperature and 5N HCl (1mL) is added. The mixture is diluted with diethyl ether and extracted with 1N HCl. The organic layer is washed with water and brine, then dried over anhydrous sodium sulfate. Concentration of the solvent reveals the {3-[2-(4-Trifluoromethyl-phenyl)-5,6-dihydro-4H-cyclopentathiazol-4-ylmethoxy]-phenyl}-acetic acid (158 mg, 0,3645 mmol)

The following compounds are made in a substantially similar manner:

Example 16

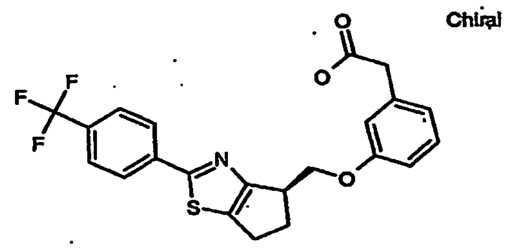
<u>(S)-{3-[2-(4-Trifluoromethyl-phenyl)-5,6-dihydro-4H-cyclopentathiazol-4-ylmethoxy]-phenyl}-acetic acid</u>



MS (ES): 434.06(M^{+}+1).

Example 17

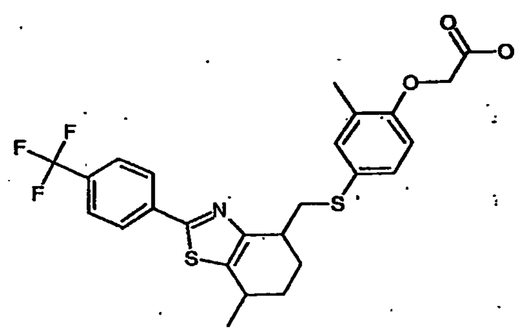
<u>(R)-{3-[2-(4-Trifluoromethyl-phenyl)-5,6-dihydro-4H-cyclopentathiazol-4-ylmethoxy]-phenyl}-acetic acid</u>



MS (ES): 434.06(M^{+}+1).

Example 18

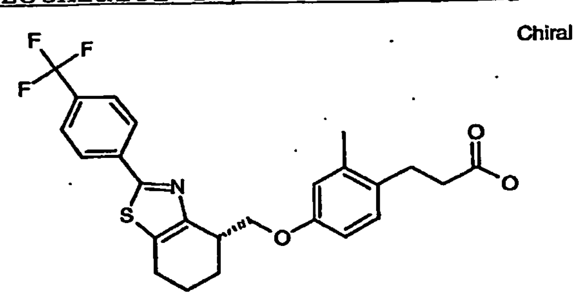
{2-Methyl-4-[7-methyl-2-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-benzothiazol-4-ylmethylsulfanyl]-phenoxy}-acetic acid



MS (ES): 508.15(M^{+}+1).

Example 19

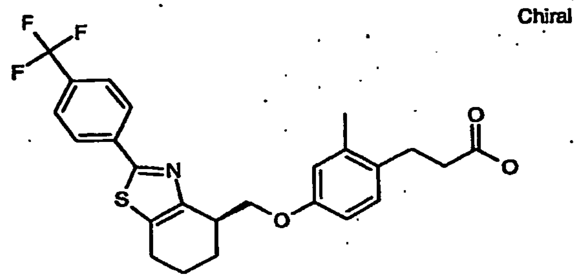
(S)-3-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-benzothiazol-4-ylmethoxy]-phenyl}-propionic acid



MS (ES): 476.08(M^{+}+1).

Example 20

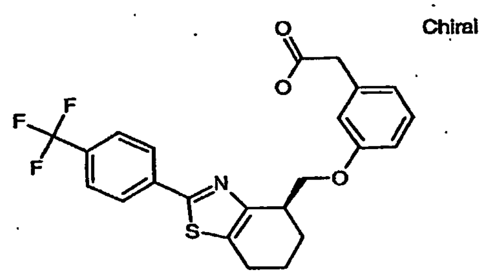
(R)-3-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-benzothiazol-4-ylmethoxy]-phenyl}-propionic acid



MS (ES): 476.07(M^{+}+1).

Example 21

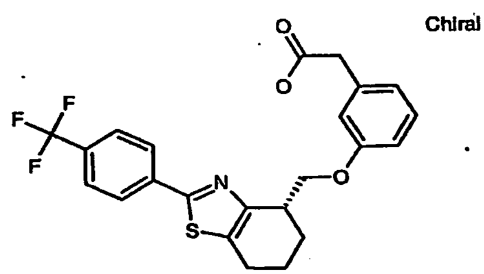
(R)-{3-[2-(4-Trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-benzothiazol-4-ylmethoxy]-phenyl}-acetic acid



MS (ES): 448.07(M^{+}+1).

Example 22

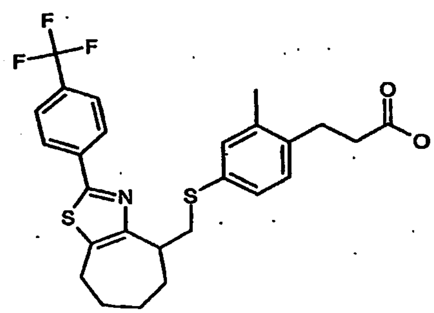
(S)-{3-[2-(4-Trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-benzothiazol-4-ylmethoxy]-phenyl}-acetic acid



MS (ES): 448.07(M^{+}+1).

Example 23

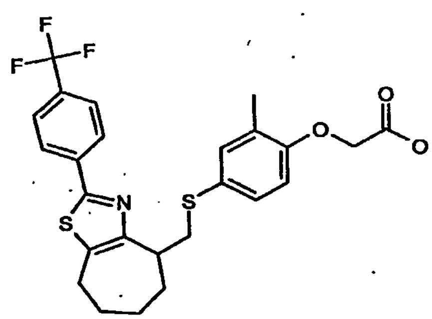
3-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-5,6,7,8-tetrahydro-4H-cycloheptathiazol-4-ylmethylsulfanyl]-phenyl}-propionic acid



MS (ES): 506.13(M^{+}+1).

Example 24

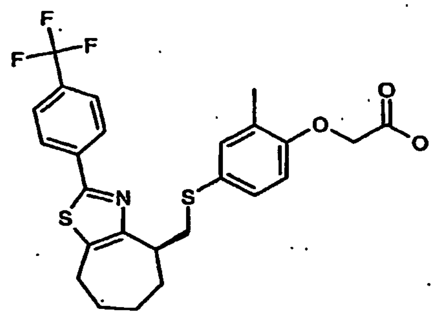
{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-5,6,7,8-tetrahydro-4H-cycloheptathiazol-4-ylmethylsulfanyl]-phenoxy}-acetic acid



MS (ES): 508.09(M^{+}+1).

Example 25

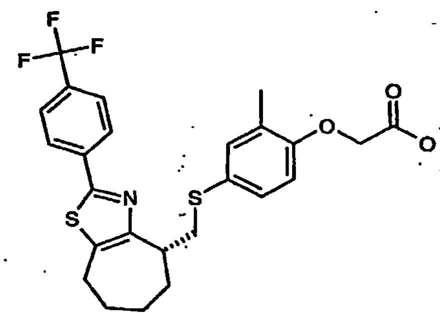
(R)-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-5,6,7,8-tetrahydro-4H-cycloheptathiazol-4-ylmethylsulfanyl]-phenoxy}-acetic acid



MS (ES): 508.1(M^{+}+1).

Example 26

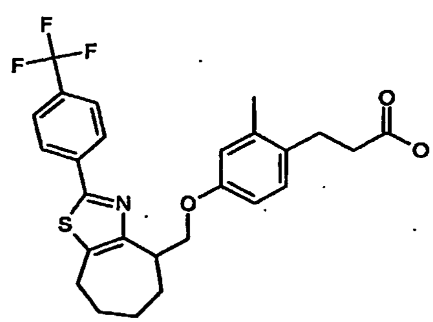
(S)-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-5,6,7,8-tetrahydro-4H-cycloheptathiazol-4-ylmethylsulfanyl]-phenoxy}-acetic acid



MS (ES): 508.1(M^{+}+1).

Example 27

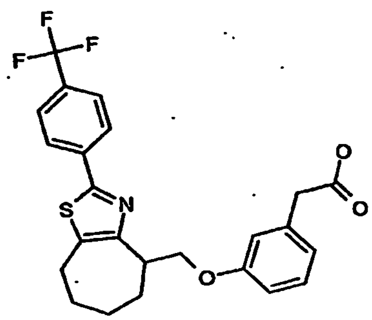
3-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-5,6,7,8-tetrahydro-4H-cycloheptathiazol-4-ylmethoxy]-phenyl}-propionic acid



MS (ES): 490.15(M^{+}+1).

Example 28

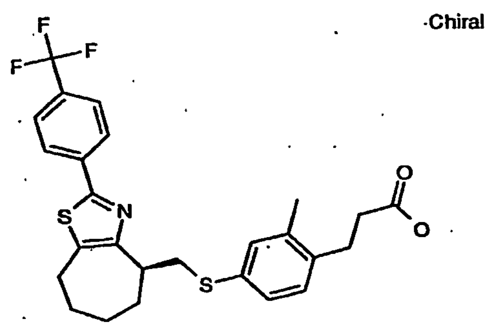
{3-[2-(4-Trifluoromethyl-phenyl)-5,6,7,8-tetrahydro-4H-cycloheptathiazol-4-ylmethoxy]-phenyl}-acetic acid



MS (ES): 462.07(M^{+}+1).

Example 29

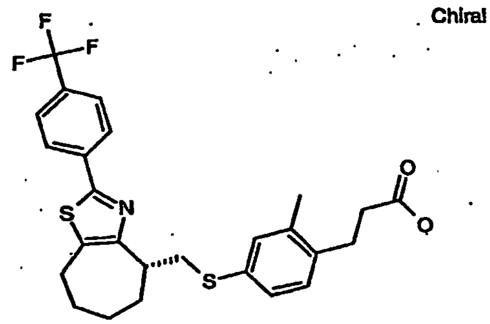
(R)-3-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-5,6,7,8-tetrahydro-4H-cycloheptathiazol-4-ylmethylsulfanyl]-phenyl}-propionic acid



MS (ES): 506.01(M^{+}+1).

Example 30

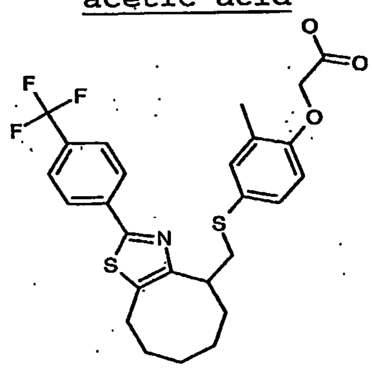
(S)-3-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-5,6,7,8-tetrahydro-4H-cycloheptathiazol-4-ylmethylsulfanyl]-phenyl}-propionic acid



MS (ES): 506.01(M^{+}+1).

Example 31

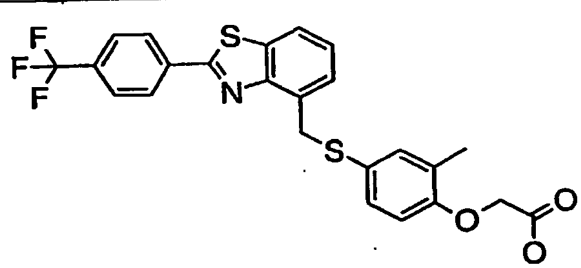
{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-4,5,6,7,8,9-hexahydro-cyclooctathiazol-4-ylmethylsulfanyl]-phenoxy}-acetic acid



MS (ES): 594.11(M^{+}+1).

Example 32

{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-benzothiazol-4-ylmethylsulfanyl]-phenoxy}-acetic acid



Step A

{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-benzothiazol-4-ylmethylsulfanyl]-phenoxy}-acetic acid ethyl ester

A solution of (4-mercapto-2-methyl-phenoxy)-acetic acid ethyl ester (113 mg, 0.5 mmol) and [2-(4-trifluoromethyl-phenyl)-benzothiazol-4-yl]-methanol (100 mg, 0.323 mmol) in toluene (3.0 mL) is degassed and filled with nitrogen for 3 times. Tributylphosphine (0.124 mL, 0.5 mmol) is added to the reaction mixture under nitrogen at 0 °C, followed by addition of of 1,1'-(azodicarbonyl)-dipiperidine (120 mg, 0.5 mmol). The reaction mixture is allowed to warm to room temperature and stirred overnight, the mixture is loaded on silica gel column. Chromatography gave the title compound (100 mg).

Step B

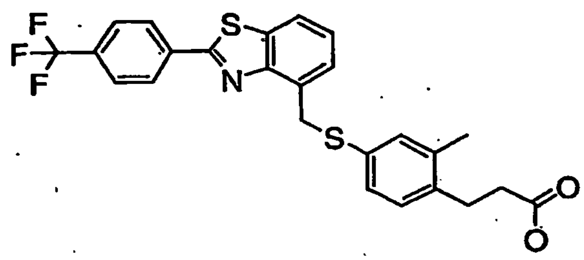
{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-benzothiazol-4-ylmethylsulfanyl]-phenoxy}-acetic acid

{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-benzothiazol-4-ylmethylsulfanyl]-phenoxy}-acetic acid ethyl ester from step A is taken into ethanol (1 mL) and treated with NaOH (5.0 N, 1 mL) for 2hrs at 50 °C. The reaction mixture is cooled to room temperature and acidified with 5 N HCl, extracted with ethyl ether, dried over sodium sulfate. Concentration yields the title compound. MS (ES): 490.1(M^++1), the structure is also confirmed by proton NMR.

The following compounds are made in a similar manner:

Example 33

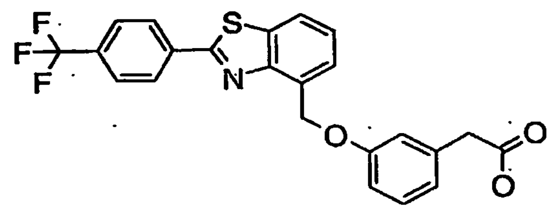
3-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-benzothiazol-4-ylmethylsulfanyl]-phenyl}-propionic acid



MS (ES): 488.1(M^{+}+1).

Example 34

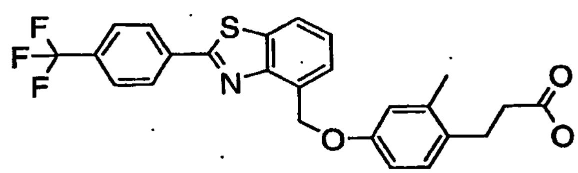
{3-[2-(4-Trifluoromethyl-phenyl)-benzothiazol-4-ylmethoxy]-phenyl}-acetic acid



MS (ES): 444.1(M^{+}+1).

Example 35

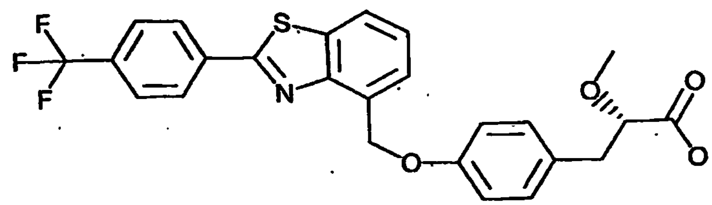
3-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-benzothiazol-4-ylmethoxy]-phenyl}-propionic acid



MS (ES): 472.1 (M^{+}+1).

Example 36

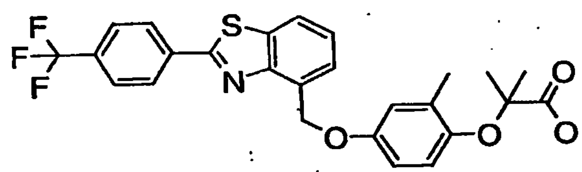
(S)-2-Methoxy-3-{4-[2-(4-trifluoromethyl-phenyl)-benzothiazol-4-ylmethoxy]-phenyl}-propionic acid



MS (ES): 472.1 (M^{+}+1).

Example 37

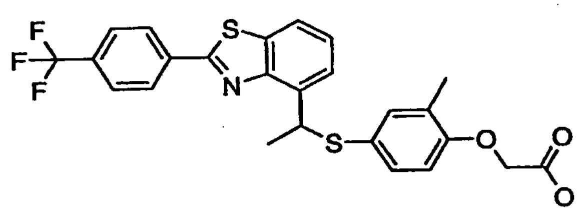
2-Methyl-2-{2-methyl-4-[2-(4-trifluoromethyl-phenyl)-benzothiazol-4-ylmethoxy]-phenoxy}-propionic acid



MS (ES): 502.2(M^{+}+1).

Example 38

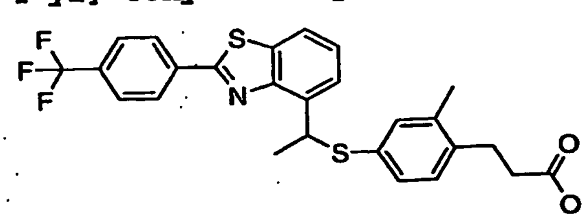
Racemic-(2-methyl-4-{1-[2-(4-trifluoromethyl-phenyl)-benzothiazol-4-yl]-ethylsulfanyl}-phenoxy)-acetic acid



MS (ES): 504.3(M^{+}+1).

Example 39

Racemic-3-(2-methyl-4-{1-[2-(4-trifluoromethyl-phenyl)-benzothiazol-4-yl]-ethylsulfanyl}-phenyl)-propionic acid



MS (ES): 502.9(M^{+}+1).

Racemic methyl ester of example 38 and 39 can be resolved by ChiralPak AD column with heptane and isopropanol alcohol (4:1) as eluent, thus enantimerically pure compounds were obtained.

Biological Assays

Binding and Cotransfection Studies

The in vitro potency of compounds in modulating PPARα receptors are determined by the procedures detailed below. DNA-dependent binding (ABCD binding) is carried out using SPA technology with PPAR receptors. Tritium-labeled PPARα agonists are used as radioligands for generating displacement curves and IC_{50} values with compounds of the invention. Cotransfection assays are carried out in CV-1 cells. The reporter plasmid contained an acylCoA oxidase (AOX) PPRE and TK promoter upstream of the luciferase reporter cDNA. Appropriate PPARs are constitutively expressed using plasmids containing the CMV promoter. For PPARα, interference by endogenous PPARγ in CV-1 cells is an issue. In order to eliminate such interference, a GAL4 chimeric system is used in which the DNA binding domain of the transfected PPAR is replaced by that of GAL4, and the GAL4 response element is utilized in place of the AOX PPRE. Cotransfection efficacy is determined relative to PPARα agonist reference molecules. Efficacies are determined by computer fit to a concentration-response curve, or in some cases at a single high concentration of agonist (10 μM).

These studies are carried out to evaluate the ability of compounds of the invention to bind to and/or activate various nuclear transcription factors, particularly huPPARα ("hu" indicates "human"). These studies provide in vitro

data concerning efficacy and selectivity of compounds of the invention. Furthermore, binding and cotransfection data for compounds of the invention are compared with corresponding data for marketed compounds that act on huPPARα.

The binding and cotransfection efficacy values for compounds of the invention which are especially useful for modulating a PPAR receptor, are $\leq$ 100 nM and $\geq$ 50%, respectively.

Evaluation of Triglyceride Reduction and HDL Cholesterol Elevation in HuapoAI Transgenic Mice

Compounds of the present invention are studied for effects upon HDL and triglyceride levels in human apoAI mice. For each compound tested, seven to eight week old male mice, transgenic for human apoAI (C57BL/6-tgn(apoa1)1rub, Jackson Laboratory, Bar Harbor, ME) are acclimated in individual cages for two weeks with standard chow diet (Purina 5001) and water provided ad libitum. After the acclimation, mice and chow are weighed and assigned to test groups (n = 5) with randomization by body weight. Mice are dosed daily by oral gavage for 8 days using a 29 gauge, 1-1/2 inch curved feeding needle (Popper & Sons). The vehicle for the controls, test compounds and the positive control (fenofibrate 100mg/kg) is 1% carboxymethylcellulose (w/v) with 0.25% tween 80 (w/v). All mice are dosed daily between 6 and 8 a.m. with a dosing volume of 0.2ml. Prior to termination, animals and diets are weighed and body weight change and food consumption are calculated. Three hours after last dose, mice are euthanized with CO2 and blood is removed (0.5-1.0 ml) by cardiac puncture. After sacrifice, the liver, heart, and epididymal fat pad are excised and weighed. Blood is

permitted to clot and serum is separated from the blood by centrifugation.

Cholesterol and triglycerides are measured colorimetrically using commercially prepared reagents (for example, as available from Sigma #339-1000 and Roche #450061 for triglycerides and cholesterol, respectively). The procedures are modified from published work (McGowan M. W. et al., Clin Chem 29:538-542,1983; Allain C. C. et al., Clin Chem 20:470-475,1974. Commercially available standards for triglycerides and total cholesterol, respectively, commercial quality control plasma, and samples are measured in duplicate using 200 µl of reagent. An additional aliquot of sample, added to a well containing 200 µl water, provided a blank for each specimen. Plates are incubated at room temperature on a plate shaker and absorbance is read at 500 nm and 540 nm for total cholesterol and triglycerides, respectively. Values for the positive control are always within the expected range and the coefficient of variation for samples is below 10%. All samples from an experiment are assayed at the same time to minimize inter-assay variability.

Serum lipoproteins are separated and cholesterol quantitated by fast protein liquid chromatography (FPLC) coupled to an in line detection system. Samples are applied to a Superose 6 HR size exclusion column (Amersham Pharmacia Biotech) and eluted with phosphate buffered saline-EDTA at 0.5 ml/min. Cholesterol reagent (Roche Diagnostics Chol/HP 704036) at 0.16ml/min mixed with the column effluent through a T-connection and the mixture passed through a 15 m x 0.5 mm id knitted tubing reactor immersed in a 37 C water bath. The colored product produced in the presence of cholesterol is monitored in the flow strem at 505 nm and the analog

voltage from the monitor is converted to a digital signal for collection and analysis. The change in voltage corresponding to change in cholesterol concentration is plotted vs time and the area under the curve corresponding to the elution of very low density lipoprotein (VLDL), low density lipoprotein (LDL) and high density lipoprotein (HDL) is calculated using Perkin Elmer Turbochrome software.

Triglyceride Serum Levels in Mice Dosed with a Compound of the Invention is Compared to Mice Receiving the Vehicle to identify compounds which could be particularly useful for lowering triglycerides. Generally, triglyceride decreases of greater than or equal to 30% (thirty percent) compared to control following a 30 mg/kg dose suggests a compound that can be especially useful for lowering triglyceride levels.

The percent increase of HDLc serum levels in mice receiving a compound of the invention is compared to mice receiving vehicle to identify compounds of the invention that could be particularly useful for elevating HDL levels. Generally, and increase of greater than or equal to 25% (twenty five percent) increase in HDLc level following a 30 mg/kg dose suggests a compound that can be especially useful for elevating HDLc levels.

It may be particularly desirable to select compounds of this invention that both lower triglyceride levels and increase HDLc levels. However, compounds that either lower triglyceride levels or increase HDLc levels may be desirable as well.

Evaluation of Glucose Levels in db/db Mice

The effects upon plasma glucose associated with administering various dose levels of different compounds of the present invention and the PPAR gamma agonist

rosiglitazone (BRL49653) or the PPAR alpha agonist fenofibrate, and the control, to male db/db mice, are studied.

Five week old male diabetic (db/db) mice [for example, C57BlKs/j-m +/+ Lepr(db), Jackson Laboratory, Bar Harbor, ME] or lean littermates are housed 6 per cage with food and water available at all times. After an acclimation period of 2 weeks, animals are individually identified by ear notches, weighed, and bled via the tail vein for determination of initial glucose levels. Blood is collected (100 µl) from unfasted animals by wrapping each mouse in a towel, cutting the tip of the tail with a scalpel, and milking blood from the tail into a heparinized capillary tube. Sample is discharged into a heparinized microtainer with gel separator and retained on ice. Plasma is obtained after centrifugation at 4ºC and glucose measured immediately. Remaining plasma is frozen until the completion of the experiment, when glucose and triglycerides are assayed in all samples. Animals are grouped based on initial glucose levels and body weights. Beginning the following morning, mice are dosed daily by oral gavage for 7 days. Treatments are test compounds (30 mg/kg), a positive control agent (30 mg/kg) or vehicle [1% carboxymethylcellulose (w/v)/ 0.25% Tween80 (w/v); 0.3 ml/mouse]. On day 7, mice are weighed and bled (tail vein) 3 hours after dosing. Twenty-four hours after the 7th dose (i.e., day 8), animals are bled again (tail vein). Samples obtained from conscious animals on days 0, 7 and 8 are assayed for glucose. After the 24-hour bleed, animals are weighed and dosed for the final time. Three hours after dosing on day 8, animals are anesthetized by inhalation of isoflurane and blood obtained via cardiac puncture (0.5-0.7

ml). Whole blood is transferred to serum separator tubes, chilled on ice and permitted to clot. Serum is obtained after centrifugation at 4°C and frozen until analysis for compound levels. After sacrifice by cervical dislocation, the liver, heart and epididymal fat pads are excised and weighed.

Glucose is measured colorimetrically using commercially purchased reagents. According to the manufacturers, the procedures are modified from published work (McGowan, M. W., Artiss, J. D., Strandbergh, D. R. & Zak, B. Clin Chem, 20:470-5 (1974) and Keston, A. Specific colorimetric enzymatic analytical reagents for glucose. Abstract of papers 129th Meeting ACS, 31C (1956).); and depend on the release of a mole of hydrogen peroxide for each mole of analyte, coupled with a color reaction first described by Trinder (Trinder, P. Determination of glucose in blood using glucose oxidase with an alternative oxygen acceptor. Ann Clin Biochem, 6:24 (1969)). The absorbance of the dye produced is linearly related to the analyte in the sample. The assays are further modified in our laboratory for use in a 96 well format. The commercially available standard for glucose, commercially available quality control plasma, and samples (2 or 5 µl/well) are measured in duplicate using 200 µl of reagent. An additional aliquot of sample, pipetted to a third well and diluted in 200 µl water, provided a blank for each specimen. Plates are incubated at room temperature for 18 minutes for glucose on a plate shaker (DPC Micormix 5) and absorbance read at 500 nm on a plate reader. Sample absorbances are compared to a standard curve (100-800 for glucose). Values for the quality control sample are always within the expected range and the coefficient of variation for samples is below 10%. All samples from an experiment

are assayed at the same time to minimize inter-assay variability.

Evaluation of the Effects of Compounds of the Present Invention upon A^y Mice Body Weight, Fat Mass, Glucose and Insulin Levels

Female A^y Mice

Female A^y mice are singly housed, maintained under standardized conditions (22°C, 12 h light:dark cycle), and provided free access to food and water throughout the duration of the study. At twenty weeks of age the mice are randomly assigned to vehicle control and treated groups based on body weight and body fat content as assessed by DEXA scanning (N=6). Mice are then dosed via oral gavage with either vehicle or a Compound of this invention (50 mg/kg) one hour after the initiation of the light cycle (for example, about 7 A.M.) for 18 days. Body weights are measured daily throughout the study. On day 14 mice are maintained in individual metabolic chambers for indirect calorimetry assessment of energy expenditure and fuel utilization. On day 18 mice are again subjected to DEXA scanning for post treatment measurement of body composition.

The results of p.o. dosing of compound for 18 days on body weight, fat mass, and lean mass are evaluated and suggest which compounds of this invention can be especially useful for maintaining desirable weight and/or promoting desired lean to fat mass.

Indirect calorimetry measurements revealing a significant reduction in respiratory quotient (RQ) in treated animals during the dark cycle [0.864 $\pm$ 0.013 (Control) vs. 0.803 $\pm$ 0.007 (Treated); $p < 0.001$] is indicative of an increased utilization of fat during the

animals' active (dark) cycle and can be used to selected especially desired compounds of this invention. Additionally, treated animals displaying significantly higher rates of energy expenditure than control animals suggest such compounds of this invention can be especially desired.

Male KK/A^y Mice

Male KK/A^y mice are singly housed, maintained under standardized conditions (22°C, 12 h light:dark cycle), and provided free access to food and water throughout the duration of the study. At twenty-two weeks of age the mice are randomly assigned to vehicle control and treated groups based on plasma glucose levels. Mice are then dosed via oral gavage with either vehicle or a Compound of this invention (30 mg/kg) one hour after the initiation of the light cycle (7 A.M.) for 14 days. Plasma glucose, triglyceride, and insulin levels are assessed on day 14.

The results of p.o. dosing of compound for 14 days on plasma glucose, triglycerides, and insulin are evaluated to identify compounds of this invention which may be especially desired.

Method to Elucidate the LDL-cholesterol Total-cholesterol and Triglyceride Lowering Effect

Male Syrian hamsters (Harlan Sprague Dawley) weighing 80-120 g are placed on a high-fat cholesterol-rich diet for two to three weeks prior to use. Feed and water are provided ad libitum throughout the course of the experiment. Under these conditions, hamsters become hypercholesterolemic showing plasma cholesterol levels between 180-280 mg/dl. (Hamsters fed with normal chow have a total plasma

cholesterol level between 100-150 mg/dl.) Hamsters with high plasma cholesterol (180 mg/dl and above) are randomized into treatment groups based on their total cholesterol level using the GroupOptimizeV211.xls program.

A Compound of this invention is dissolved in an aqueous vehicle (containing CMC with Tween 80) such that each hamster received once a day approx. 1 ml of the solution by garvage at doses 3 and 30 mg/kg body weight. Fenofibrate (Sigma Chemical, prepared as a suspension in the same vehicle) is given as a known alpha-agonist control at a dose of 200 mg/kg, and the blank control is vehicle alone. Dosing is performed daily in the early morning for 14 days.

Quantification of Plasma Lipids :

On the last day of the test, hamsters are bled (400 ul) from the suborbital sinus while under isoflurane anesthesia 2 h after dosing. Blood samples are collected into heparinized microfuge tubes chilled in ice bath. Plasma samples are separated from the blood cells by brief centrifugation. Total cholesterol and triglycerides are determined by means of enzymatic assays carried out automatically in the Monarch equipment (Instrumentation Laboratory) following the manufacturer's precedure. Plasma lipoproteins (VLDL, LDL and HDL) are resolved by injecting 25 ul of the pooled plasma samples into an FPLC system eluted with phosphate buffered saline at 0.5 ml/min through a Superose 6 HR 10/30 column (Pharmacia) maintained room temp. Detection and characterization of the isolated plasma lipids are accomplished by postcolumn incubation of the effluent with a Cholesterol/HP reagent (for example, Roche Lab System; infused at 0.12 ml/min) in a knitted reaction coil maintained at 37°C. The intensity of the color formed is

proportional to the cholesterol concentration and is measured photometrically at 505 nm.

The effect of administration of a Compound of this invention for 14 days is studied for the percent reduction in LDL level with reference to the vehicle group. Especially desired compounds are markedly more potent than fenofibrate in LDL-lowering efficacy. Compounds of this invention that decrease LDL greater than or equal to 30% (thirty percent) compared to vehicle can be especially desired.

The total-cholesterol and triglyceride lowering effects of a Compound of this invention is also studied. The data for reduction in total cholesterol and triglyceride levels after treatment with a compound of this invention for 14 days is compared to the vehicle to suggest compounds that can be particularly desired. The known control fenofibrate did not show significant efficacy under the same experimental conditions.

<u>Method to Elucidate the Fibrinogen-Lowering Effect of PPAR Modulators</u>

Zucker Fatty Rat Model:

The life phase of the study on fibrinogen-lowering effect of compounds of this invention is part of the life phase procedures for the antidiabetic studies of the same compounds. On the last (14th) day of the treatment period, with the animals placed under surgical anesthesia, ~ 3ml of blood is collected, by cardiac puncture, into a syringe containing citrate buffer. The blood sample is chilled and centrifuged at 4°C to isolate the plasma that is stored at -70 °C prior to fibrinogen assay.

Quantification of Rat Plasma Fibrinogen:

Rat plasma fibrinogen levels are quantified by using a commercial assay system consists of a coagulation instrument following the manufacturer's protocol. In essence, 100 ul of plasma is sampled from each specimen and a 1/20 dilution is prepared with buffer. The diluted plasma is incubated at 37°C for 240 seconds. Fifty microliters of clotting reagent thrombin solution (provided by the instrument's manufacturer in a standard concentration) is then added. The instrument monitors the clotting time, a function of fibrinogen concentration quantified with reference to standard samples. Compounds that lower fibrinogen level greater than vehicle can be especially desired.

Cholesterol and triglyceride lowering effects of compounds of this invention are also studied in Zucker rats.

Method to Elucidate the Anti-body Weight Gain and Anti-appetite Effects of Compounds of this invention

Fourteen-Day Study in Zucker Fatty Rat[1] or ZDF Rat[2] Models :

Male Zucker Fatty rats, non-diabetic (Charles River Laboratories, Wilmington, MA) or male ZDF rats (Genetic Models, Inc, Indianapolis, IN) of comparable age and weight are acclimated for 1 week prior to treatment. Rats are on normal chow and water is provided ad libitum throughout the course of the experiment.

Compounds of this invention are dissolved in an aqueous vehicle such that each rat received once a day approximately 1 ml of the solution by garvage at doses 0.1, 0.3, 1 and 3 mg/kg body weight. Fenofibrate (Sigma Chemical, prepared as a suspension in the same vehicle) a known alpha-agonist

given at doses of 300 mg/kg, as well as the vehicle are controls. Dosing is performed daily in the early morning for 14 days. Over the course of the experiment, body weight and food consumption are monitored.

Using this assay, compounds of this invention are identified to determine which can be associated with a significant weight reduction.

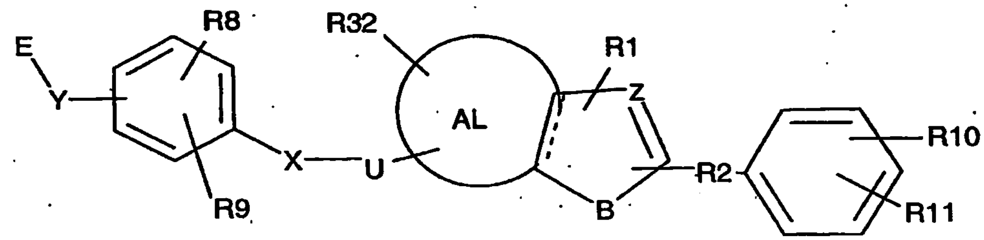
EQUIVALENTS:

While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

CLAIMS

What is claimed is:

1. A compound of the Formula I:



and stereoisomers, pharmaceutically acceptable salts, solvates and hydrates thereof, wherein:

(a) R1 is selected from the group consisting of hydrogen, C_1-C_8 alkyl, C_1-C_8 alkenyl, aryl-C_{0-4}-alkyl, aryl-C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, C3-C6 cycloalkylaryl-C_{0-2}-alkyl, and, wherein C_1-C_8 alkyl, C_1-C_8 alkenyl, aryl-C_{0-4}-alkyl, aryl-C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, C3-C6 cycloalkylaryl-C_{0-2}-alkyl are each optionally substituted with from one to three substituents independently selected from R1′;

(b) R1′, R26, R27, R28 and R31 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkyl-COOR12, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkyloxy, C_3-C_7 cycloalkyl, aryloxy, aryl-C_{0-4}-alkyl, heteroaryl, heterocycloalkyl, C(O)R13, COOR14, OC(O)R15, $OS(O)_2R16$, $N(R17)_2$, NR18C(O)R19, $NR20SO_2R21$, SR22, S(O)R23, $S(O)_2R24$, and $S(O)_2N(R25)_2$; R12, R13, R14, R15, R16, R17, R18, R19, R20, R21, R22, R23, R24 and R25 are each

independently selected from the group consisting of hydrogen, C_1-C_6 alkyl and aryl;

(c) R2 is selected from the group consisting of C_0-C_8 alkyl and C_{1-4}-heteroalkyl;

(d) X is selected from the group consisting of a single bond, O, S, $S(O)_2$ and N;

(e) U is an aliphatic linker wherein one carbon atom of the aliphatic linker may be replaced with O, NH or S, and wherein such aliphatic linker is optionally substituted with R30;

(f) Y is selected from the group consisting of C, O, S, NH and a single bond;

(g) E is C(R3)(R4)A or A and wherein

(i) A is selected from the group consisting of carboxyl, tetrazole, C_1-C_6 alkylnitrile, carboxamide, sulfonamide and acylsulfonamide; wherein sulfonamide, acylsulfonamide and tetrazole are each optionally substituted with from one to two groups independently selected from R^7;

(ii) each R^7 is independently selected from the group consisting of hydrogen, C_1-C_6 haloalkyl, aryl C_0-C_4 alkyl and C_1-C_6 alkyl;

(iii) R3 is selected from the group consisting of hydrogen, C_1-C_5 alkyl, and C_1-C_5 alkoxy; and

(iv) R4 is selected from the group consisting of H, C_1-C_5 alkyl, C_1-C_5 alkoxy, aryloxy, C_3-C_6 cycloalkyl, and aryl C_0-C_4 alkyl, and R3 and R4 are optionally combined to form a C_3-C_4 cycloalkyl, and wherein alkyl, alkoxy, aryloxy, cycloalkyl and aryl-alkyl are each optionally

substituted with one to three substituents each independently selected from R26;

(h) B is selected from the group consisting of S, O, C, and N, with the proviso that when B is N then Z is C;

(i) Z is selected from the group consisting of N and C, with the proviso that when B is C then Z is N;

(j) R8 is selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_1-C_4 alkylenyl, and halo;

(k) R9 is selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_1-C_4 alkylenyl, halo, aryl-C_0-C_4 alkyl, heteroaryl, C_1-C_6 allyl, and OR29, and wherein aryl-C_0-C_4 alkyl, heteroaryl are each optionally substituted with from one to three independently selected from R27; R29 is selected from the group consisting of hydrogen and C_1-C_4 alkyl;

(l) R10, R11 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkyl-COOR12'', C_0-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 haloalkyloxy, C_3-C_7 cycloalkyl, aryl-C_{0-4}-alkyl, aryl- C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, C3-C6 cycloalkylaryl-C_{0-2}-alkyl, aryloxy, C(O)R13', COOR14', OC(O)R15', $OS(O)_2R16'$, $N(R17')_2$, NR18'C(O)R19', $NR20'SO_2R21'$, SR22', S(O)R23', $S(O)_2R24'$, and $S(O)_2N(R25')_2$; and wherein aryl-C_{0-4}-alkyl, aryl- C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl are each optionally substituted with from one to three substituents independently selected from R28;

(m) R12′, R12′′, R13′, R14′, R15′, R16′, R17′, R18′, R19′, R20′, R21′, R22′, R23′, R24′, and R25′ are each independently selected from the group consisting of hydrogen, C_1-C_6 alkyl and aryl;

(n) R30 is selected from the group consisting of C_1-C_6 alkyl, aryl-C_{0-4}-alkyl, aryl- C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl, and wherein C_1-C_6 alkyl, aryl-C_{0-4}-alkyl, aryl- C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, and C3-C6 cycloalkylaryl-C_{0-2}-alkyl are each optionally substituted with from one to three substituents each independently selected from R31;

(o) R32 is selected from the group consisting of a bond, hydrogen, halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, and C_1-C_6 alkyloxo;

(p) AL is selected from the group consisting of a fused C_3-C_8 carbocyclic and a fused phenyl; and

(q) ---- is optionally a bond to form a double bond at the indicated position.

2. A compound as claimed by Claim 1 wherein X is -O-.

3. A compound as claimed by Claims 1 wherein X is -S-.

4. A compound as claimed by any one of Claims 1 through 3 wherein Y is O.

5. A compound as claimed by any one of Claims 1 through 3 wherein Y is C.

6. A compound as claimed by any one of Claims 1 through 3 wherein wherein Y is S.

7. A compound as claimed by any one of Claims 1 through 6 wherein Z is N.

8. A compound as claimed by any one of Claims 1 through 7 wherein B is S or O.

9. A compound as claimed by any one of Claims 1 through 6, wherein B is N.

10. A compound as claimed by any one of Claims 1 through 9 wherein AL is a fused phenyl.

11. A compound as claimed by any one of Claims one through 9 wherein AL is a fused cycloalkyl;

12. A compound as claimed by any one of Claims 1 through 9 or Claim 11 wherein ---- is a bond to form a double bond at the designated location on Formula I.

13. A compound as claimed by any one of Claims 1 through 12 wherein E is C(R3)(R4)A.

14. A compound as claimed by any one of Claims 1 through 12 wherein E is A.

15. A compound as claimed by any one of Claims 1 through 14 wherein A is COOH.

16. A compound as claimed by any one of Claims 1 through 15 wherein R10 is haloalkyl.

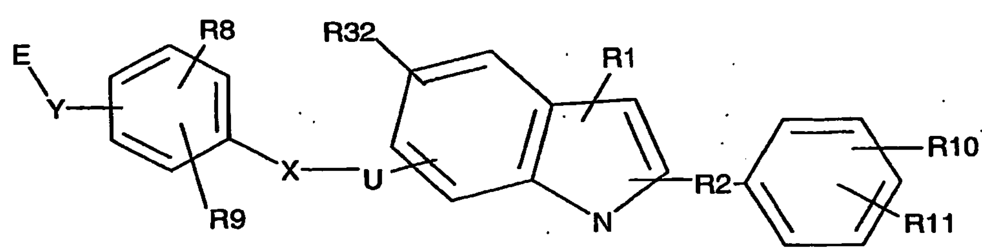
17. A compound as claimed by any one of Claims 1 through 16 wherein R10 is CF_3.

18. A compound as claimed by any one of Claims 1 through 15 wherein R10 is haloalkyloxy.

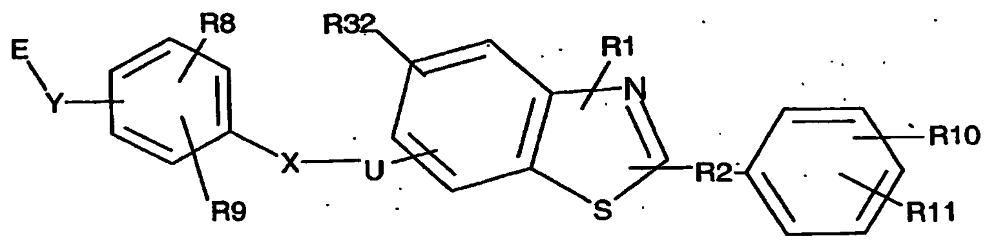
19. A compound as claimed by any one of Claims 1 through 15 wherein R10 and R11 are each independently selected from the group consisting of hydrogen, halo, oxo, C_1-C_6 alkyl, C_1-C_6 alkyl-COOR12'', C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and C_1-C_6 haloalkyloxy.

20. A compound as claimed by any one of Claims 1 through 15 wherein R10 is selected from the group consisting of C_3-C_7 cycloalkyl, aryl-C_{0-4}-alkyl, aryl-C_{1-4}-heteroalkyl, heteroaryl-C_{0-4}-alkyl, C3-C6 cycloalkylaryl-C_{0-2}-alkyl, and aryloxy.

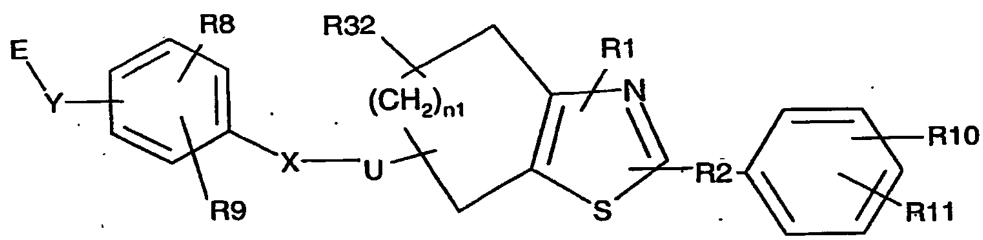
21. A compound as claimed by any one of Claims 1 through 20, wherein R8 and R9 are each independently selected from the group consisting of hydrogen and C_1-C_3 alkyl.
22. A compound as claimed by any one of Claims 1 through 21 wherein R1, R2, R3, and R4 are each independently selected from the group consisting of C_1-C_2 alkyl.
23. A compound as claimed by any one of Claims 1 through 21 wherein R1, R3, and R4 are each independently selected from the group consisting of hydrogen and C_1-C_2 alkyl.
24. A compound as claimed by any one of Claims 1 through 21 or Claim 22 wherein R2 is a bond.
25. A compound as claimed by any one of Claims 1 through 23 wherein U is C_1-C_3 alkyl.
26. A compound as claimed by Claim 25 wherein U is saturated.
27. A compound as claimed by any one of Claims 25 or 26 wherein U is substituted with C_1-C_3 alkyl.
28. A compound as claimed by any one of Claims 25, 26 or 27 wherein one carbon is replaced with an -O-.
29. A compound as claimed by any one of Claims 1 through 6, 9, 10, or one of Claims 13 through 28 of the Structural Formula II:



30. A compound as claimed by any one of Claims 1 through 8, 10, or one of Claims 13 through 28 of the Structural Formula III:



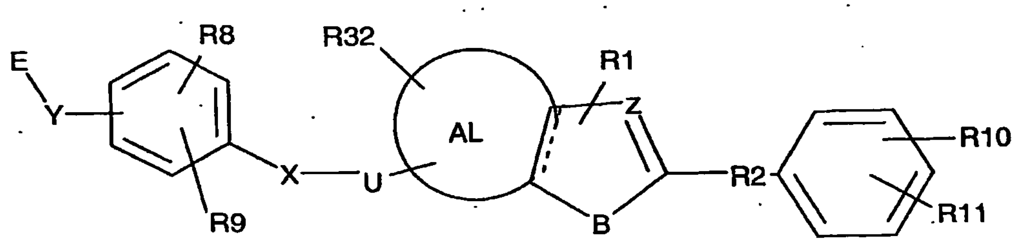
31. A compound as claimed by any one of Claims 1 through 8, or one of Claims 11 through 28 of the Structural Formula IV:



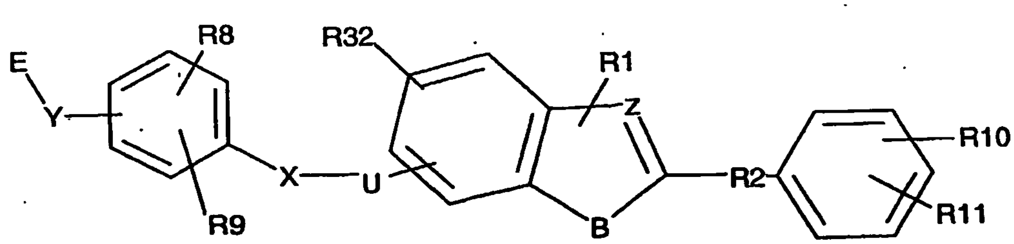
;

wherein n1 is 1 to 5.

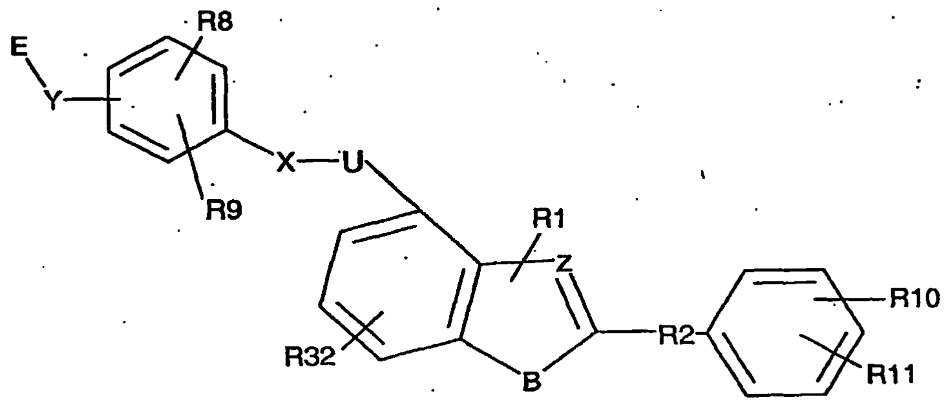
32. A compound as claimed by any one of Claims 1 through 31 of the Structural Formula V:



33. A compound as claimed by any one of Claims 1 through 10, or one of Claims 13 through 28 of the Structural Formula VI:



34. A compound as claimed by any one of Claims 1 through 10, or one of Claims 13 through 28 of the Structural Formula VII:



35. A compound as claimed by any one of Claims 33 or 35 wherein X is S, Y is selected from the group consisting of C and O, E is CH_2COOH, and R2 is a bond.

36. A compound as claimed by any one of Claims 33, 34 or 35 wherein Z is N and B is S.

37. A compound as claimed by any one of Claims 1 through 36 wherein R32 is hydrogen, R8 is hydrogen and R9 is C_1-C_4 alkyl.

38. A compound as claimed by Claim 1 wherein the compound is selected from the group consisting of

Racemic-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-5,6-dihydro-4H-cyclopentathiazol-4-ylmethylsulfanyl]-phenoxy}-acetic acid;

(R)-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-5,6-dihydro-4H-cyclopentathiazol-4-ylmethylsulfanyl]-phenoxy}-acetic acid;

(S)-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-5,6-dihydro-4H-cyclopentathiazol-4-ylmethylsulfanyl]-phenoxy}-acetic acid;

Racemic-3-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-5,6-dihydro-4H-cyclopentathiazol-4-ylmethoxy]-phenyl}-propionic acid;

Racemic-3-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-5,6-dihydro-4H-cyclopentathiazol-4-ylmethylsulfanyl]-phenyl}-propionic acid;

(R)-3-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-5,6-dihydro-4H-cyclopentathiazol-4-ylmethylsulfanyl]-phenyl}-propionic acid;

(S)-3-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-5,6-dihydro-4H-cyclopentathiazol-4-ylmethylsulfanyl]-phenyl}-propionic acid;

Racemic-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-benzothiazol-4-ylmethylsulfanyl]-phenoxy}-acetic acid;

(S)-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-benzothiazol-4-ylmethylsulfanyl]-phenoxy}-acetic acid;

(R)-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-benzothiazol-4-ylmethylsulfanyl]-phenoxy}-acetic acid;

{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-benzothiazol-4-ylmethoxy]-phenoxy}-acetic acid;

Racemic-3-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-benzothiazol-4-ylmethylsulfanyl]-phenyl}-propionic acid;

(R)-3-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-benzothiazol-4-ylmethylsulfanyl]-phenyl}-propionic acid;

(S)-3-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-benzothiazol-4-ylmethylsulfanyl]-phenyl}-propionic acid;

{3-[2-(4-Trifluoromethyl-phenyl)-5,6-dihydro-4H-cyclopentathiazol-4-ylmethoxy]-phenyl}-acetic acid;

(S)-{3-[2-(4-Trifluoromethyl-phenyl)-5,6-dihydro-4H-cyclopentathiazol-4-ylmethoxy]-phenyl}-acetic acid;

(R)-{3-[2-(4-Trifluoromethyl-phenyl)-5,6-dihydro-4H-cyclopentathiazol-4-ylmethoxy]-phenyl}-acetic acid;

{2-Methyl-4-[7-methyl-2-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-benzothiazol-4-ylmethylsulfanyl]-phenoxy}-acetic acid;

(S)-3-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-benzothiazol-4-ylmethoxy]-phenyl}-propionic acid;

(R)-3-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-benzothiazol-4-ylmethoxy]-phenyl}-propionic acid;

(R)-{3-[2-(4-Trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-benzothiazol-4-ylmethoxy]-phenyl}-acetic acid;

(S)-{3-[2-(4-Trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-benzothiazol-4-ylmethoxy]-phenyl}-acetic acid;

3-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-5,6,7,8-tetrahydro-4H-cycloheptathiazol-4-ylmethylsulfanyl]-phenyl}-propionic acid;

{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-5,6,7,8-tetrahydro-4H-cycloheptathiazol-4-ylmethylsulfanyl]-phenoxy}-acetic acid;

(R)-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-5,6,7,8-tetrahydro-4H-cycloheptathiazol-4-ylmethylsulfanyl]-phenoxy}-acetic acid;

(S)-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-5,6,7,8-tetrahydro-4H-cycloheptathiazol-4-ylmethylsulfanyl]-phenoxy}-acetic acid;

3-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-5,6,7,8-tetrahydro-4H-cycloheptathiazol-4-ylmethoxy]-phenyl}-propionic acid;

{3-[2-(4-Trifluoromethyl-phenyl)-5,6,7,8-tetrahydro-4H-cycloheptathiazol-4-ylmethoxy]-phenyl}-acetic acid;

(R)-3-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-5,6,7,8-tetrahydro-4H-cycloheptathiazol-4-ylmethylsulfanyl]-phenyl}-propionic acid;

(S)-3-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-5,6,7,8-tetrahydro-4H-cycloheptathiazol-4-ylmethylsulfanyl]-phenyl}-propionic acid;

{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-4,5,6,7,8,9-hexahydro-cyclooctathiazol-4-ylmethylsulfanyl]-phenoxy}-acetic acid;

{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-benzothiazol-4-ylmethylsulfanyl]-phenoxy}-acetic acid;

{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-benzothiazol-4-ylmethylsulfanyl]-phenoxy}-acetic acid ethyl ester;

3-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-benzothiazol-4-ylmethylsulfanyl]-phenyl}-propionic acid;

{3-[2-(4-Trifluoromethyl-phenyl)-benzothiazol-4-ylmethoxy]-phenyl}-acetic acid;

3-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-benzothiazol-4-ylmethoxy]-phenyl}-propionic acid;
(S)-2-Methoxy-3-{4-[2-(4-trifluoromethyl-phenyl)-benzothiazol-4-ylmethoxy]-phenyl}-propionic acid;
2-Methyl-2-{2-methyl-4-[2-(4-trifluoromethyl-phenyl)-benzothiazol-4-ylmethoxy]-phenoxy}-propionic acid;
Racemic-(2-methyl-4-{1-[2-(4-trifluoromethyl-phenyl)-benzothiazol-4-yl]-ethylsulfanyl}-phenoxy)-acetic acid; and
Racemic-3-(2-methyl-4-{1-[2-(4-trifluoromethyl-phenyl)-benzothiazol-4-yl]-ethylsulfanyl}-phenyl)-propionic acid.

39. A compound as claimed by Claim 1 which is selected from the group consisting of {2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-benzothiazol-4-ylmethylsulfanyl]-phenoxy}-acetic acid and 3-{2-Methyl-4-[2-(4-trifluoromethyl-phenyl)-benzothiazol-4-ylmethylsulfanyl]-phenyl}-propionic acid.

40. A compound as claimed by any one of Claims 1 through 39 which is the S conformation.

41. A compound as claimed by any one of Claims 1 through 39 which is the R conformation.

42. A pharmaceutical composition, comprising as an active ingredient, at least one compound as claimed by any one of Claims 1 through 41 together with a pharmaceutically acceptable carrier or diluent.

43. A method of modulating a peroxisome proliferator activated receptor, comprising the step of contacting the receptor with at least one compound as claimed by any one of Claims 1 through 41.

44. A method of treating diabetes mellitus in a mammal, comprising the step of administering to the mammal

in need thereof a therapeutically effective amount of at least one compound of Claims 1 through 41.

45. A method of treating Syndrome X in a mammal, comprising the step of administering to the mammal in need thereof a therapeutically effective amount of at least one compound of Claims 1 through 41.

46. A method of selectively modulating a PPAR delta receptor comprising administering a compound as claimed by any one of Claims 1 through 41 to a mammal in need thereof.

47. The manufacture of a medicament for use in the treatment and/or prevention of a condition mediated by nuclear receptors, in particular by a peroxisome proliferator activated receptor, wherein the compound is a compound as claimed by any one of Claims 1 through 41.

48. A method of treating atherosclerosis in a mammal, comprising the step of administering to the mammal in need thereof a therapeutically effective amount of at least one compound of Claims 1 through 41.

49. A compound as Claimed by any one of Claims 1 through 41 for use as a pharmaceutical.

50. A compound as claimed by any one of Claims 1 through 41 wherein the compound is radiolabeled.

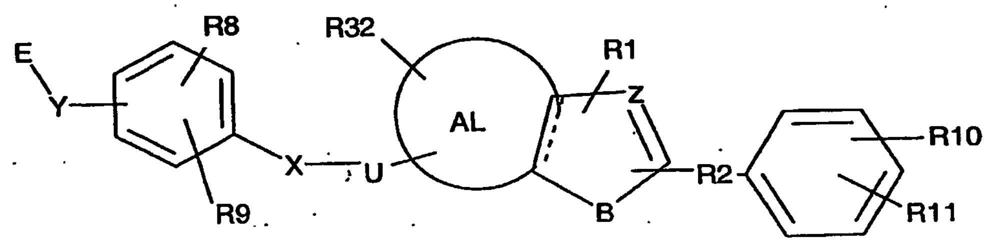
51. A compound as disclosed by any one of the Examples herein.

52. All methods disclosed herein of preparing the compounds represented by Structural Formula I.

FUSED HETEROCYCLIC DERIVATIVES AS PPAR MODULATORS

ABSTRACT OF THE DISCLOSURE

The present invention is directed to compounds represented by the following structural formula, Formula I:



wherein:

(a) X is selected from the group consisting of a single bond, O, S, $S(O)_2$ and N;

(b) U is an aliphatic linker;

(c) Y is selected from the group consisting of C, O, S, NH and a single bond;

(d) E is C(R3)(R4)A or A and wherein

(i) A is selected from the group consisting of carboxyl, tetrazole, C_1-C_6 alkylnitrile, carboxamide, sulfonamide and acylsulfonamide;

(e) B is selected from the group consisting of S, O, C, and N, with the proviso that when B is N then Z is C;

(f) Z is selected from the group consisting of N and C, with the proviso that when B is C then Z is N;

(g) R8 is selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_1-C_4 alkylenyl, and halo;

(h) R9 is selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_1-C_4 alkylenyl, halo, aryl-C_0-C_4 alkyl, heteroaryl, C_1-C_6 allyl, and OR29.